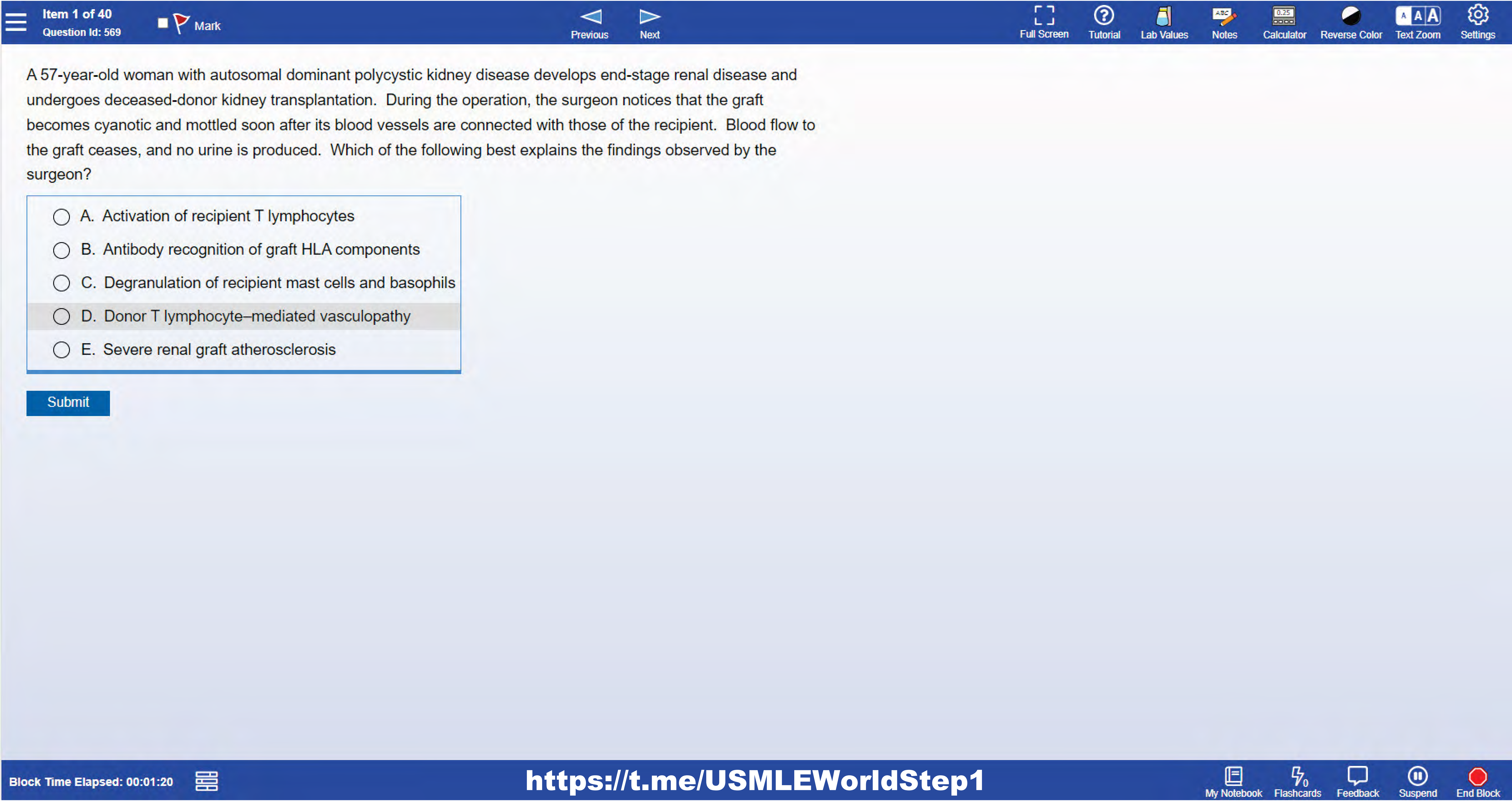
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A 57-year-old woman with autosomal dominant polycystic kidney disease develops end-stage renal disease and undergoes deceased-donor kidney transplantation. During the operation, the surgeon notices that the graft becomes cyanotic and mottled soon after its blood vessels are connected with those of the recipient. Blood flow to the graft ceases, and no urine is produced. Which of the following best explains the findings observed by the surgeon?

- ○ A. Activation of recipient T lymphocytes
- ○ B. Antibody recognition of graft HLA components
- ○ C. Degranulation of recipient mast cells and basophils
- ○ D. Donor T lymphocyte–mediated vasculopathy
- ○ E. Severe renal graft atherosclerosis

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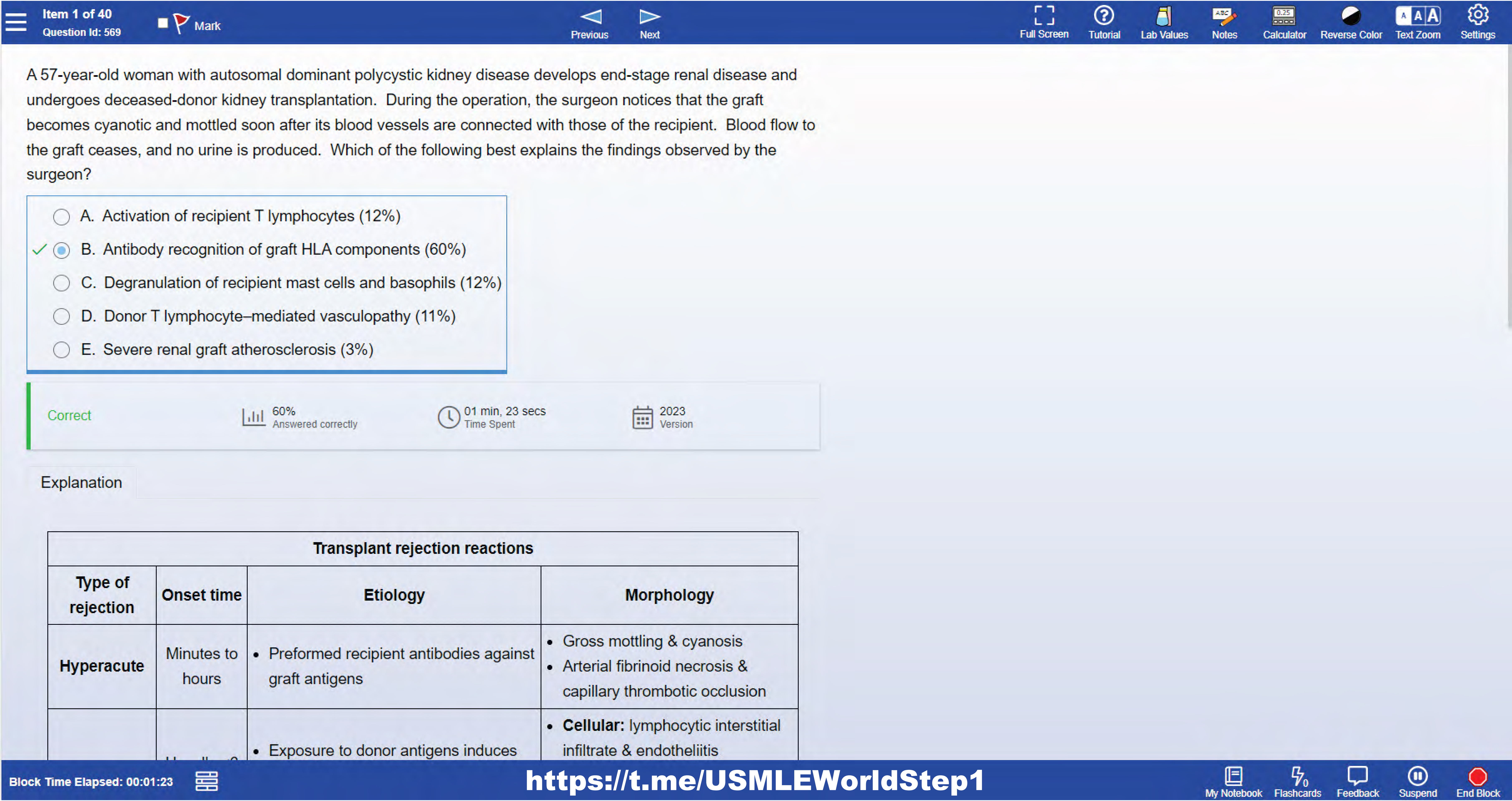
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○ A. Activation of recipient T lymphocytes (12%)
✓ ● B. Antibody recognition of graft HLA components (60%)
○ C. Degranulation of recipient mast cells and basophils (12%)
○ D. Donor T lymphocyte–mediated vasculopathy (11%)
○ E. Severe renal graft atherosclerosis (3%)

Correct

60%
Answered correctly

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Explanation

Transplant rejection reactions			
Type of rejection	**Onset time**	**Etiology**	**Morphology**
Hyperacute	Minutes to hours	• Preformed recipient antibodies against graft antigens	• Gross mottling & cyanosis • Arterial fibrinoid necrosis & capillary thrombotic occlusion
		• Exposure to donor antigens induces	• **Cellular:** lymphocytic interstitial infiltrate & endotheliitis

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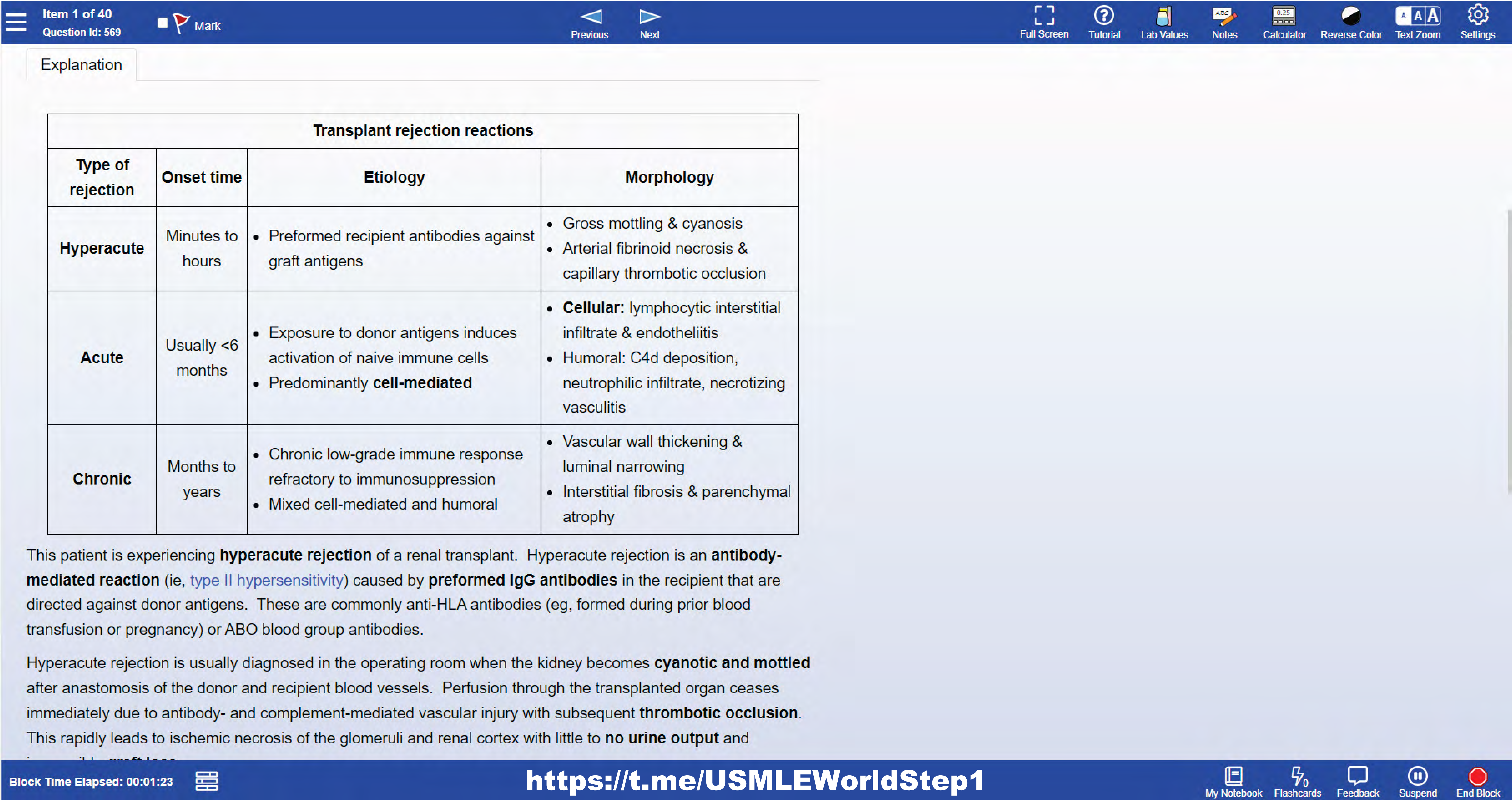
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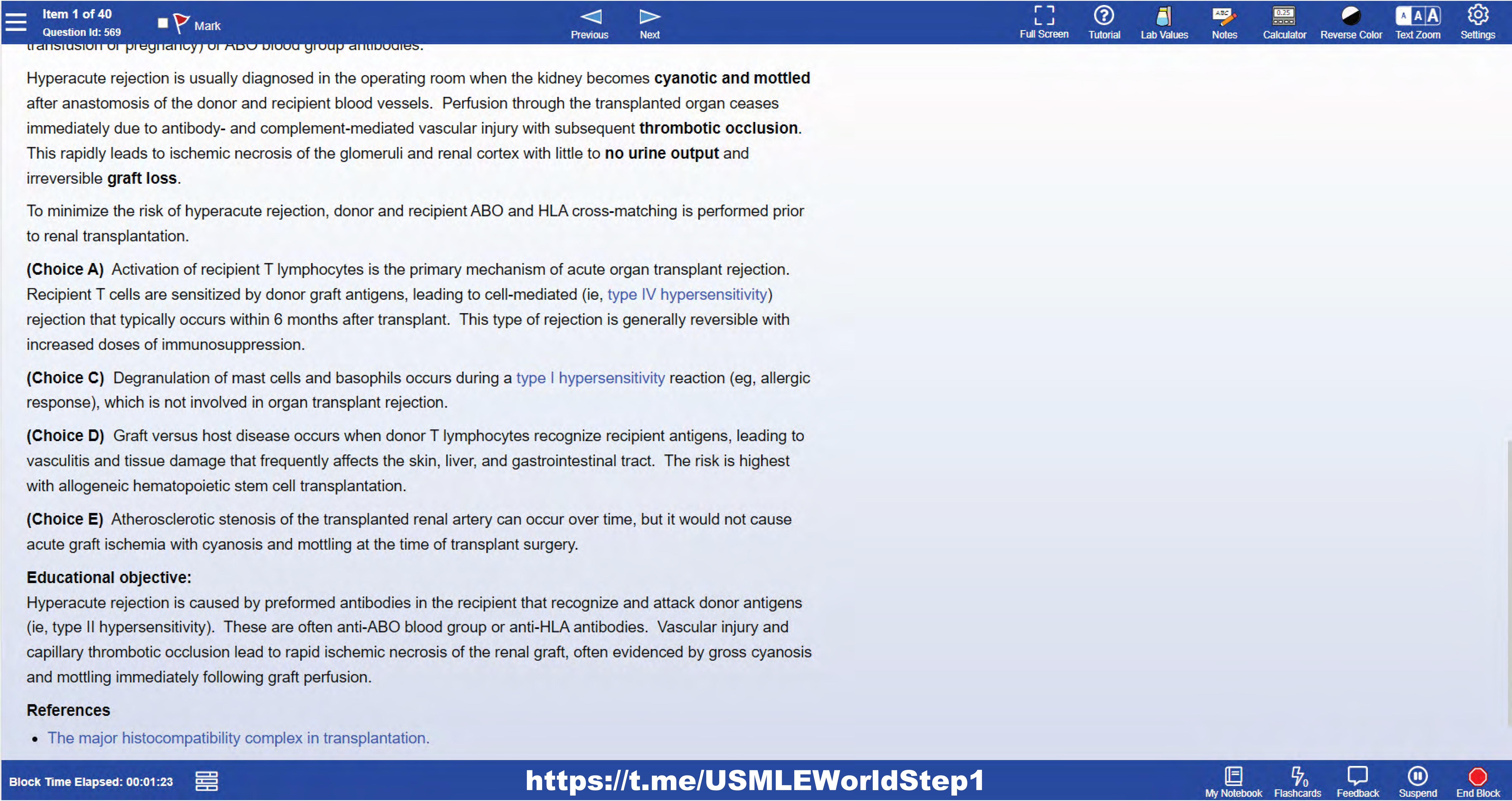
Transplant rejection reactions

Type of rejection	Onset time	Etiology	Morphology
Hyperacute	Minutes to hours	• Preformed recipient antibodies against graft antigens	• Gross mottling & cyanosis • Arterial fibrinoid necrosis & capillary thrombotic occlusion
Acute	Usually <6 months	• Exposure to donor antigens induces activation of naive immune cells • Predominantly **cell-mediated**	• **Cellular:** lymphocytic interstitial infiltrate & endotheliitis • Humoral: C4d deposition, neutrophilic infiltrate, necrotizing vasculitis
Chronic	Months to years	• Chronic low-grade immune response refractory to immunosuppression • Mixed cell-mediated and humoral	• Vascular wall thickening & luminal narrowing • Interstitial fibrosis & parenchymal atrophy

This patient is experiencing **hyperacute rejection** of a renal transplant. Hyperacute rejection is an **antibody-mediated reaction** (ie, type II hypersensitivity) caused by **preformed IgG antibodies** in the recipient that are directed against donor antigens. These are commonly anti-HLA antibodies (eg, formed during prior blood transfusion or pregnancy) or ABO blood group antibodies.

Hyperacute rejection is usually diagnosed in the operating room when the kidney becomes **cyanotic and mottled** after anastomosis of the donor and recipient blood vessels. Perfusion through the transplanted organ ceases immediately due to antibody- and complement-mediated vascular injury with subsequent **thrombotic occlusion**. This rapidly leads to ischemic necrosis of the glomeruli and renal cortex with little to **no urine output** and



transfusion or pregnancy) of ABO blood group antibodies.

Hyperacute rejection is usually diagnosed in the operating room when the kidney becomes **cyanotic and mottled** after anastomosis of the donor and recipient blood vessels. Perfusion through the transplanted organ ceases immediately due to antibody- and complement-mediated vascular injury with subsequent **thrombotic occlusion**. This rapidly leads to ischemic necrosis of the glomeruli and renal cortex with little to **no urine output** and irreversible **graft loss**.

To minimize the risk of hyperacute rejection, donor and recipient ABO and HLA cross-matching is performed prior to renal transplantation.

(Choice A) Activation of recipient T lymphocytes is the primary mechanism of acute organ transplant rejection. Recipient T cells are sensitized by donor graft antigens, leading to cell-mediated (ie, type IV hypersensitivity) rejection that typically occurs within 6 months after transplant. This type of rejection is generally reversible with increased doses of immunosuppression.

(Choice C) Degranulation of mast cells and basophils occurs during a type I hypersensitivity reaction (eg, allergic response), which is not involved in organ transplant rejection.

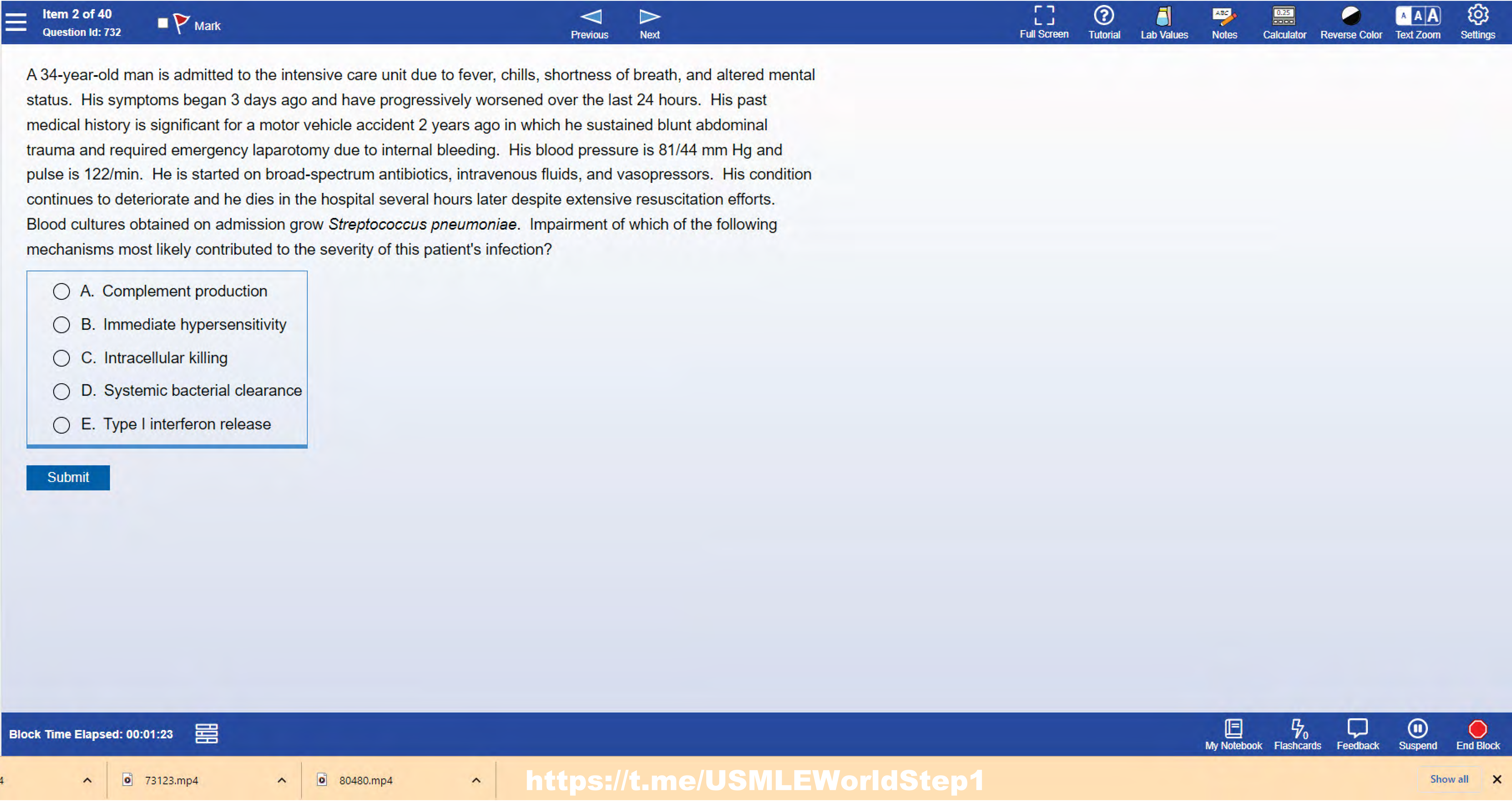
(Choice D) Graft versus host disease occurs when donor T lymphocytes recognize recipient antigens, leading to vasculitis and tissue damage that frequently affects the skin, liver, and gastrointestinal tract. The risk is highest with allogeneic hematopoietic stem cell transplantation.

(Choice E) Atherosclerotic stenosis of the transplanted renal artery can occur over time, but it would not cause acute graft ischemia with cyanosis and mottling at the time of transplant surgery.

Educational objective:
Hyperacute rejection is caused by preformed antibodies in the recipient that recognize and attack donor antigens (ie, type II hypersensitivity). These are often anti-ABO blood group or anti-HLA antibodies. Vascular injury and capillary thrombotic occlusion lead to rapid ischemic necrosis of the renal graft, often evidenced by gross cyanosis and mottling immediately following graft perfusion.

References

- The major histocompatibility complex in transplantation.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A 34-year-old man is admitted to the intensive care unit due to fever, chills, shortness of breath, and altered mental status. His symptoms began 3 days ago and have progressively worsened over the last 24 hours. His past medical history is significant for a motor vehicle accident 2 years ago in which he sustained blunt abdominal trauma and required emergency laparotomy due to internal bleeding. His blood pressure is 81/44 mm Hg and pulse is 122/min. He is started on broad-spectrum antibiotics, intravenous fluids, and vasopressors. His condition continues to deteriorate and he dies in the hospital several hours later despite extensive resuscitation efforts. Blood cultures obtained on admission grow *Streptococcus pneumoniae*. Impairment of which of the following mechanisms most likely contributed to the severity of this patient's infection?

- ○ A. Complement production
- ○ B. Immediate hypersensitivity
- ○ C. Intracellular killing
- ○ D. Systemic bacterial clearance
- ○ E. Type I interferon release

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- ○ A. Complement production (25%)
- ✗ ● B. Immediate hypersensitivity (1%)
- ○ C. Intracellular killing (10%)
- ✓ ○ D. Systemic bacterial clearance (58%)
- ○ E. Type I interferon release (3%)

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Correct answer
D

58%
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Explanation

Anatomy of the spleen

Capillaries allow blood into red pulp reticular meshwork

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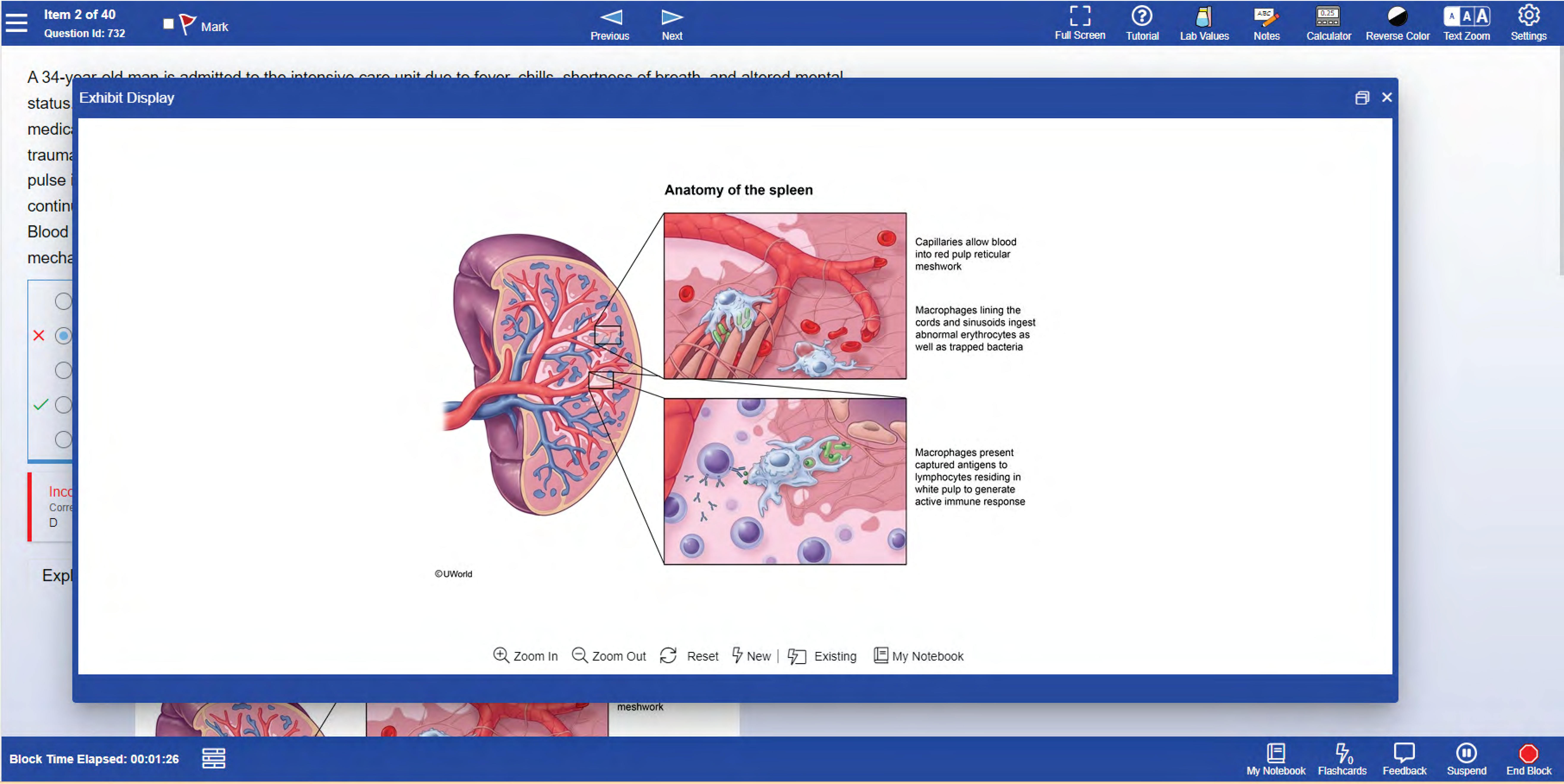
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A 34-year old man is admitted to the intensive care unit due to fever, chills, shortness of breath, and altered mental
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Anatomy of the spleen

Capillaries allow blood into red pulp reticular meshwork

Macrophages lining the cords and sinusoids ingest abnormal erythrocytes as well as trapped bacteria

Macrophages present captured antigens to lymphocytes residing in white pulp to generate active immune response

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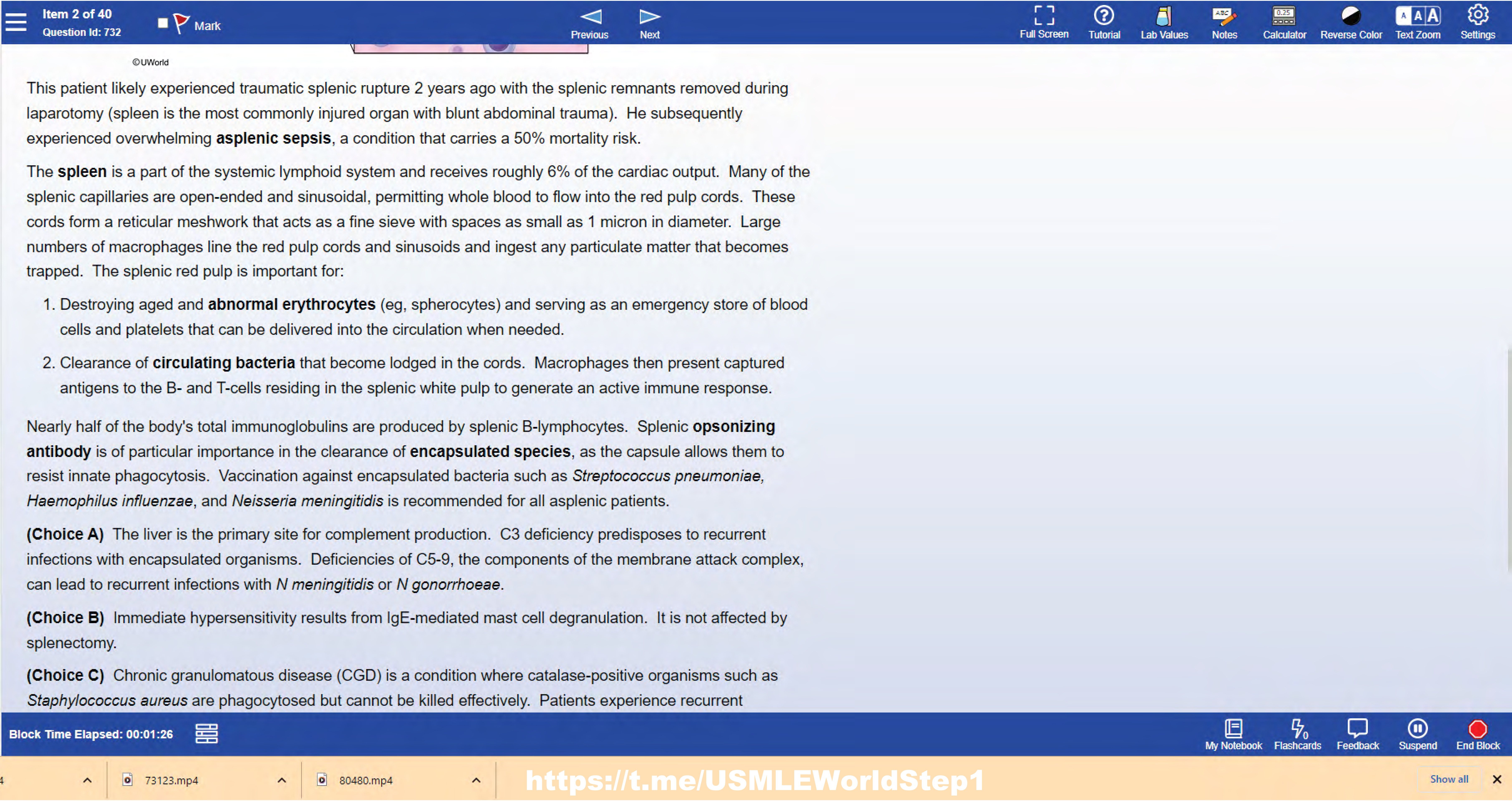

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This patient likely experienced traumatic splenic rupture 2 years ago with the splenic remnants removed during laparotomy (spleen is the most commonly injured organ with blunt abdominal trauma). He subsequently experienced overwhelming **asplenic sepsis**, a condition that carries a 50% mortality risk.

The **spleen** is a part of the systemic lymphoid system and receives roughly 6% of the cardiac output. Many of the splenic capillaries are open-ended and sinusoidal, permitting whole blood to flow into the red pulp cords. These cords form a reticular meshwork that acts as a fine sieve with spaces as small as 1 micron in diameter. Large numbers of macrophages line the red pulp cords and sinusoids and ingest any particulate matter that becomes trapped. The splenic red pulp is important for:

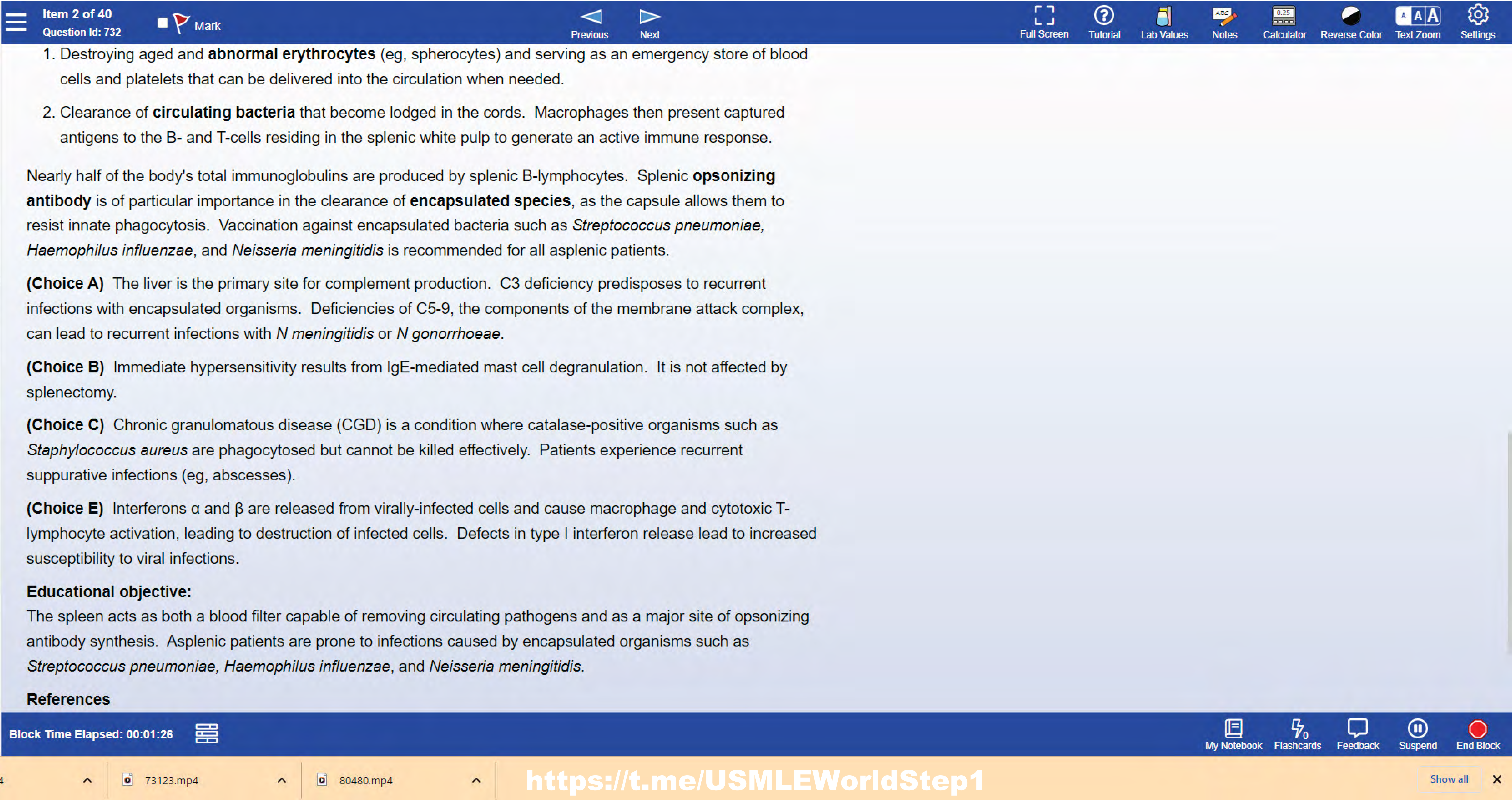
1. Destroying aged and **abnormal erythrocytes** (eg, spherocytes) and serving as an emergency store of blood cells and platelets that can be delivered into the circulation when needed.
2. Clearance of **circulating bacteria** that become lodged in the cords. Macrophages then present captured antigens to the B- and T-cells residing in the splenic white pulp to generate an active immune response.

Nearly half of the body's total immunoglobulins are produced by splenic B-lymphocytes. Splenic **opsonizing antibody** is of particular importance in the clearance of **encapsulated species**, as the capsule allows them to resist innate phagocytosis. Vaccination against encapsulated bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae*, and *Neisseria meningitidis* is recommended for all asplenic patients.

(Choice A) The liver is the primary site for complement production. C3 deficiency predisposes to recurrent infections with encapsulated organisms. Deficiencies of C5-9, the components of the membrane attack complex, can lead to recurrent infections with *N meningitidis* or *N gonorrhoeae*.

(Choice B) Immediate hypersensitivity results from IgE-mediated mast cell degranulation. It is not affected by splenectomy.

(Choice C) Chronic granulomatous disease (CGD) is a condition where catalase-positive organisms such as *Staphylococcus aureus* are phagocytosed but cannot be killed effectively. Patients experience recurrent



1. Destroying aged and **abnormal erythrocytes** (eg, spherocytes) and serving as an emergency store of blood cells and platelets that can be delivered into the circulation when needed.
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(Choice B) Immediate hypersensitivity results from IgE-mediated mast cell degranulation. It is not affected by splenectomy.

(Choice C) Chronic granulomatous disease (CGD) is a condition where catalase-positive organisms such as *Staphylococcus aureus* are phagocytosed but cannot be killed effectively. Patients experience recurrent suppurative infections (eg, abscesses).

(Choice E) Interferons α and β are released from virally-infected cells and cause macrophage and cytotoxic T-lymphocyte activation, leading to destruction of infected cells. Defects in type I interferon release lead to increased susceptibility to viral infections.

Educational objective:
The spleen acts as both a blood filter capable of removing circulating pathogens and as a major site of opsonizing antibody synthesis. Asplenic patients are prone to infections caused by encapsulated organisms such as *Streptococcus pneumoniae, Haemophilus influenzae*, and *Neisseria meningitidis*.

References

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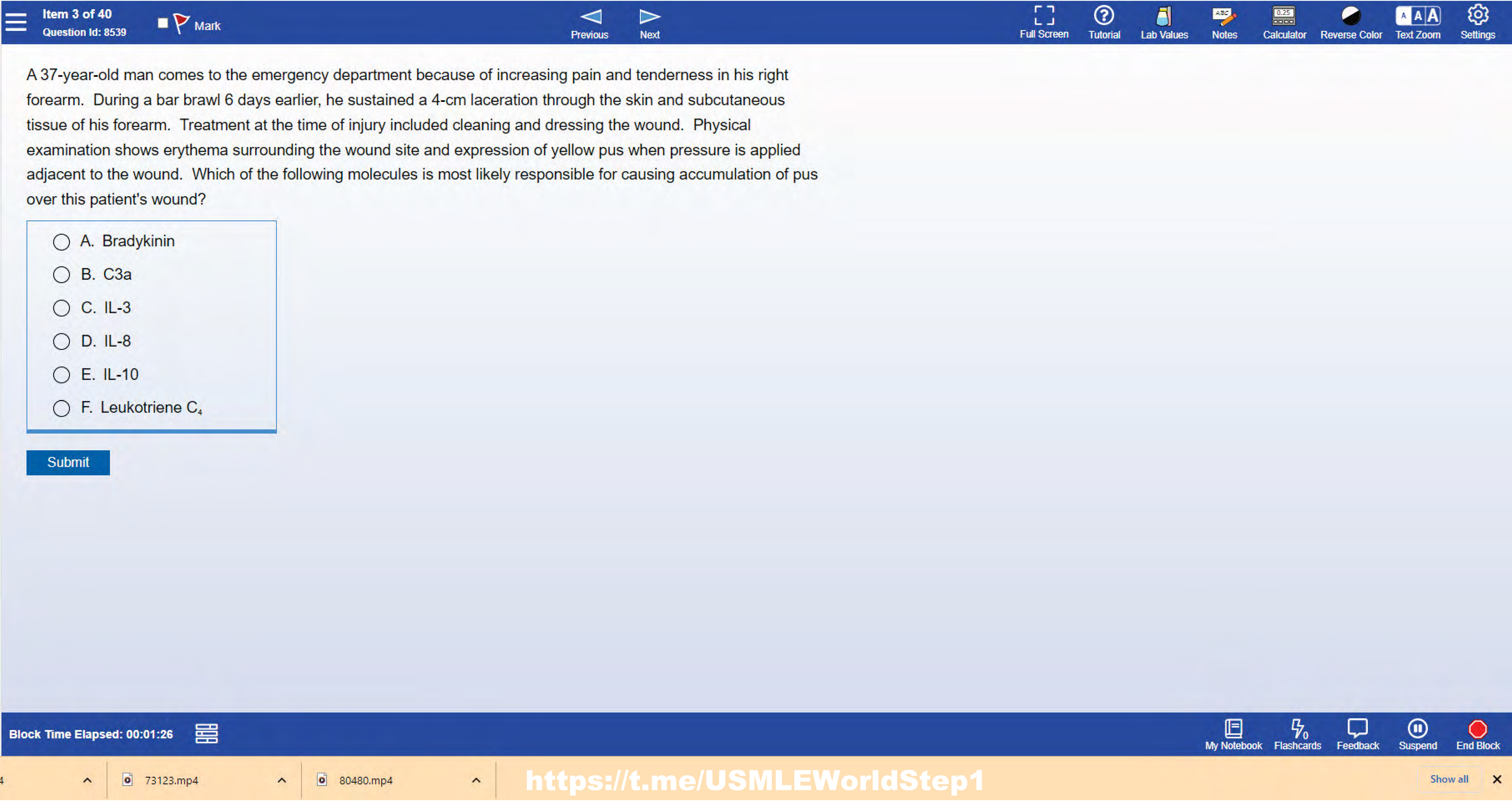
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A 37-year-old man comes to the emergency department because of increasing pain and tenderness in his right forearm. During a bar brawl 6 days earlier, he sustained a 4-cm laceration through the skin and subcutaneous tissue of his forearm. Treatment at the time of injury included cleaning and dressing the wound. Physical examination shows erythema surrounding the wound site and expression of yellow pus when pressure is applied adjacent to the wound. Which of the following molecules is most likely responsible for causing accumulation of pus over this patient's wound?

○ A. Bradykinin
○ B. C3a
○ C. IL-3
○ D. IL-8
○ E. IL-10
○ F. Leukotriene C_4

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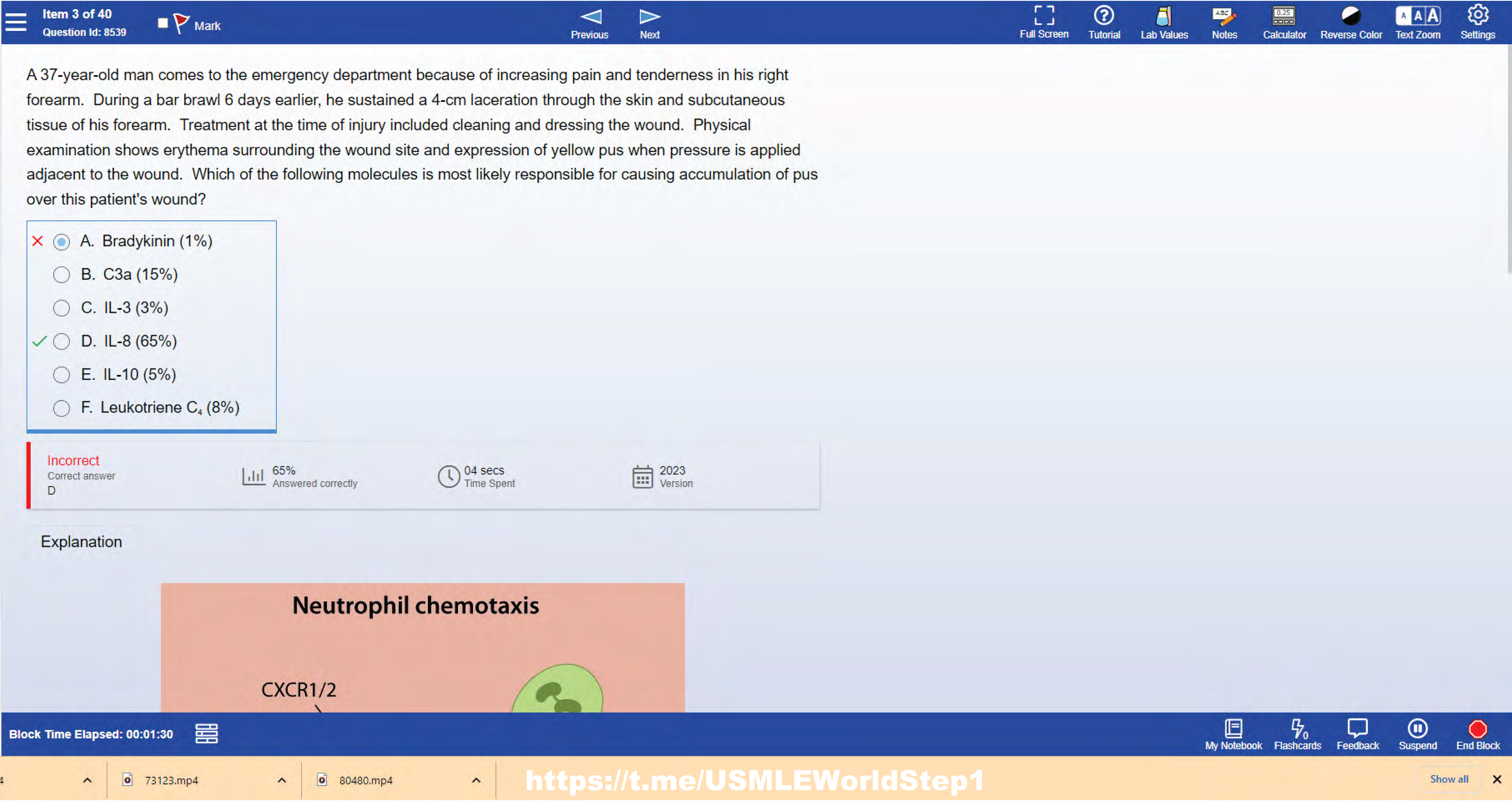
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- ✗ ● A. Bradykinin (1%)
- ○ B. C3a (15%)
- ○ C. IL-3 (3%)
- ✓ ○ D. IL-8 (65%)
- ○ E. IL-10 (5%)
- ○ F. Leukotriene C_4 (8%)

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Correct answer
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65%
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Explanation

Neutrophil chemotaxis

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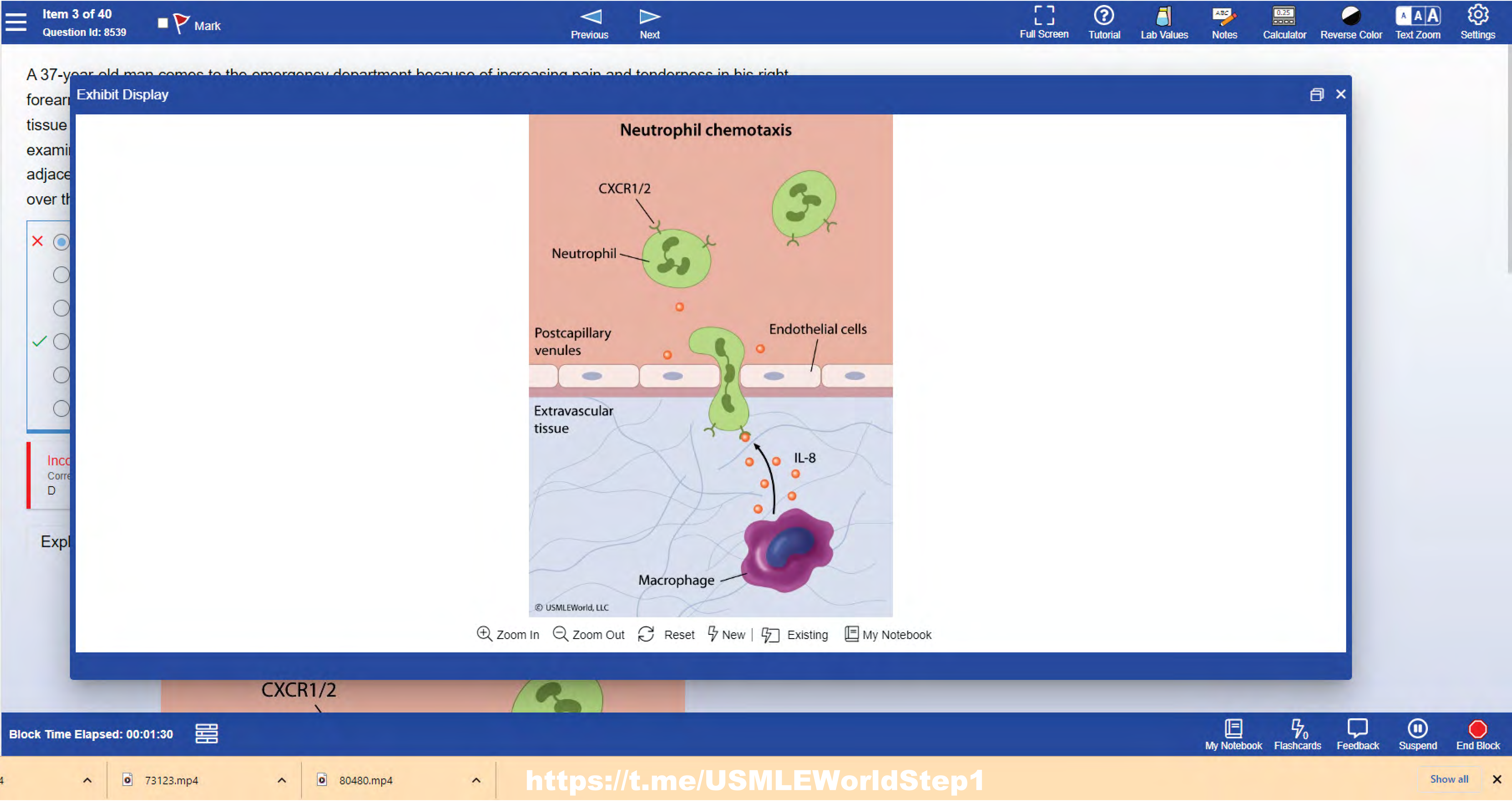
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Neutrophil chemotaxis

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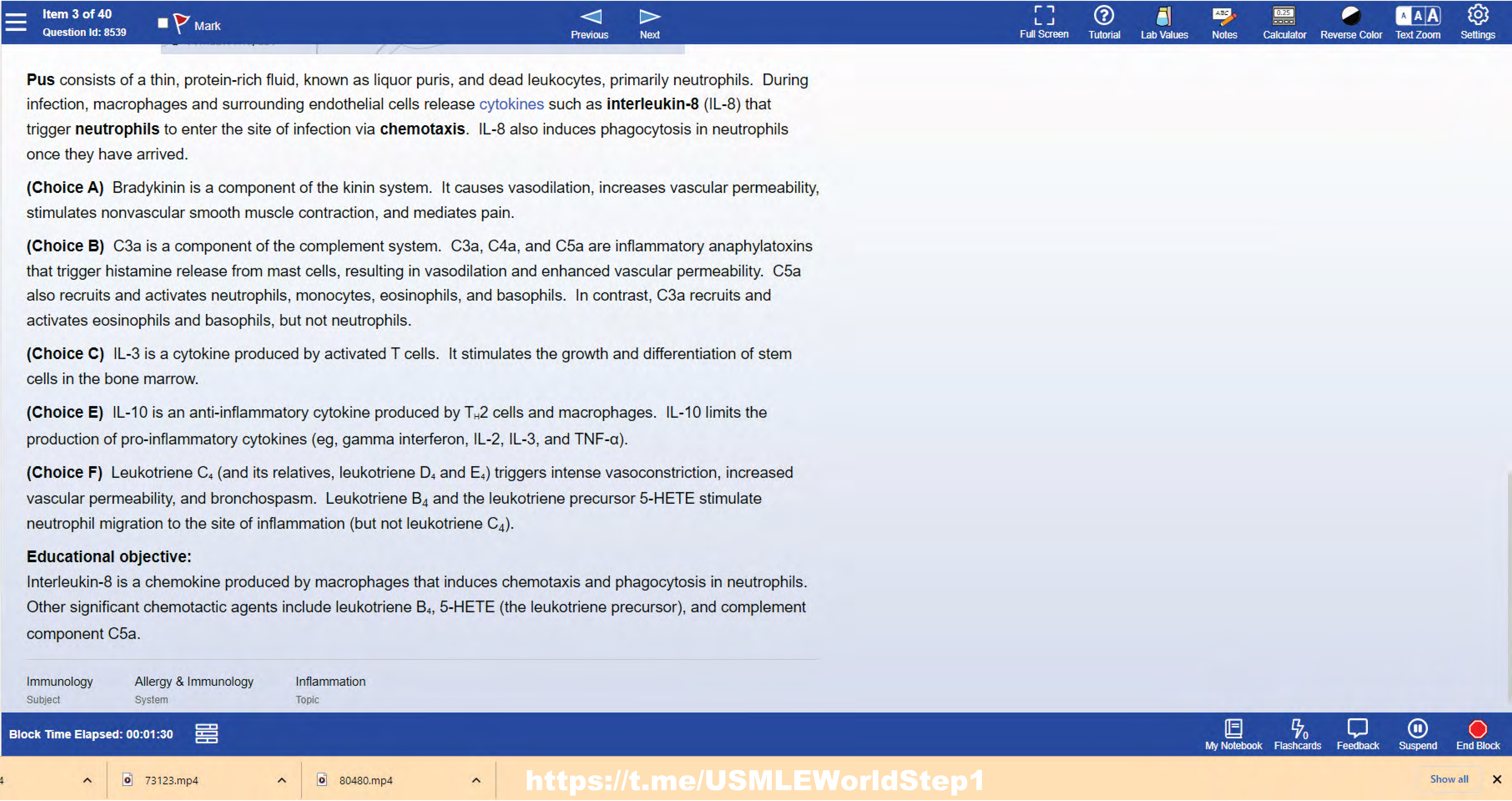
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Pus consists of a thin, protein-rich fluid, known as liquor puris, and dead leukocytes, primarily neutrophils. During infection, macrophages and surrounding endothelial cells release cytokines such as **interleukin-8** (IL-8) that trigger **neutrophils** to enter the site of infection via **chemotaxis**. IL-8 also induces phagocytosis in neutrophils once they have arrived.

(Choice A) Bradykinin is a component of the kinin system. It causes vasodilation, increases vascular permeability, stimulates nonvascular smooth muscle contraction, and mediates pain.

(Choice B) C3a is a component of the complement system. C3a, C4a, and C5a are inflammatory anaphylatoxins that trigger histamine release from mast cells, resulting in vasodilation and enhanced vascular permeability. C5a also recruits and activates neutrophils, monocytes, eosinophils, and basophils. In contrast, C3a recruits and activates eosinophils and basophils, but not neutrophils.

(Choice C) IL-3 is a cytokine produced by activated T cells. It stimulates the growth and differentiation of stem cells in the bone marrow.

(Choice E) IL-10 is an anti-inflammatory cytokine produced by T_H2 cells and macrophages. IL-10 limits the production of pro-inflammatory cytokines (eg, gamma interferon, IL-2, IL-3, and TNF-α).

(Choice F) Leukotriene C_4 (and its relatives, leukotriene D_4 and E_4) triggers intense vasoconstriction, increased vascular permeability, and bronchospasm. Leukotriene B_4 and the leukotriene precursor 5-HETE stimulate neutrophil migration to the site of inflammation (but not leukotriene C_4).

Educational objective:
Interleukin-8 is a chemokine produced by macrophages that induces chemotaxis and phagocytosis in neutrophils. Other significant chemotactic agents include leukotriene B_4, 5-HETE (the leukotriene precursor), and complement component C5a.

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Subject	System	Topic

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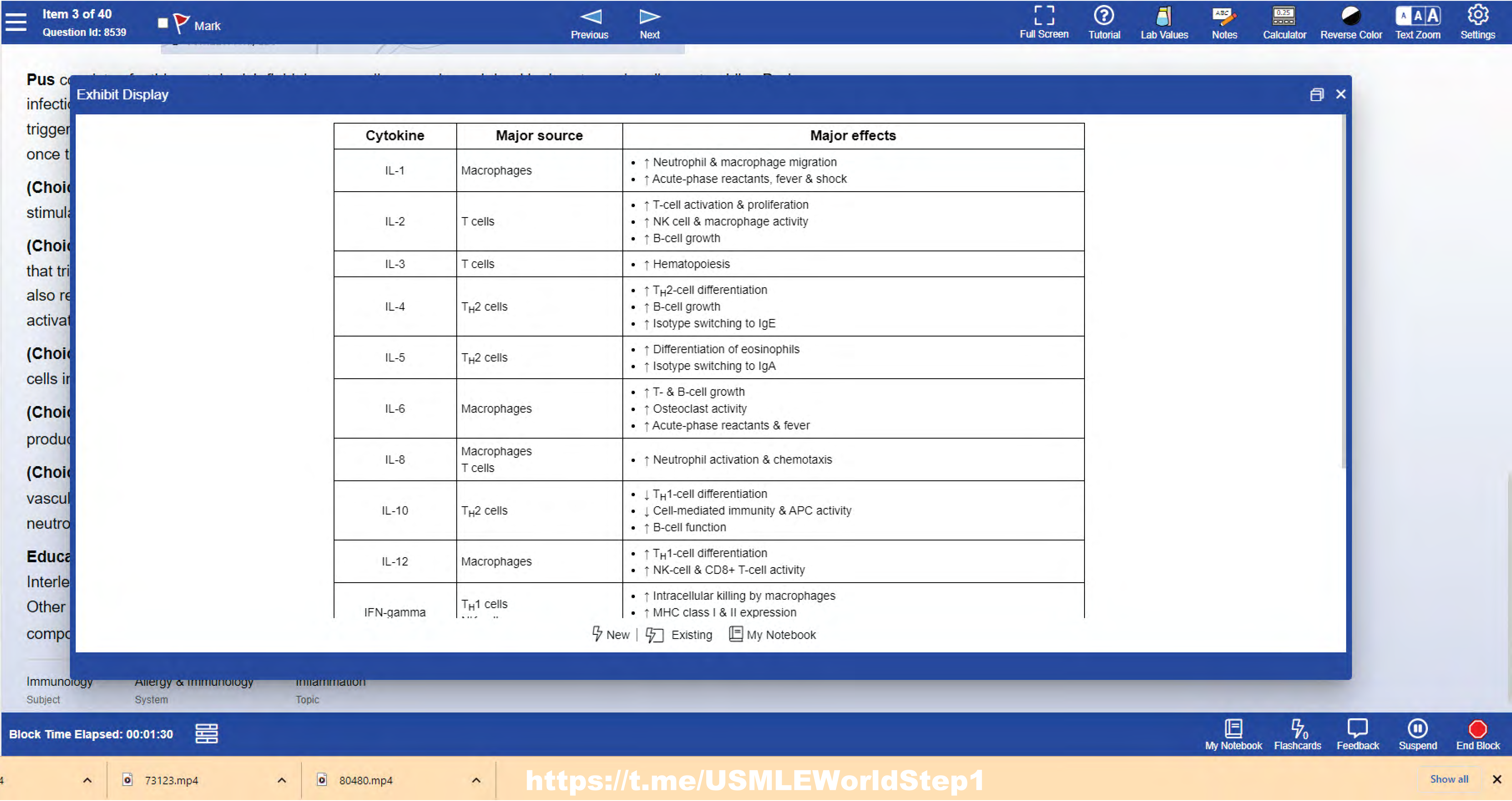
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Cytokine	Major source	Major effects
IL-1	Macrophages	• ↑ Neutrophil & macrophage migration • ↑ Acute-phase reactants, fever & shock
IL-2	T cells	• ↑ T-cell activation & proliferation • ↑ NK cell & macrophage activity • ↑ B-cell growth
IL-3	T cells	• ↑ Hematopoiesis
IL-4	T_H2 cells	• ↑ T_H2-cell differentiation • ↑ B-cell growth • ↑ Isotype switching to IgE
IL-5	T_H2 cells	• ↑ Differentiation of eosinophils • ↑ Isotype switching to IgA
IL-6	Macrophages	• ↑ T- & B-cell growth • ↑ Osteoclast activity • ↑ Acute-phase reactants & fever
IL-8	Macrophages T cells	• ↑ Neutrophil activation & chemotaxis
IL-10	T_H2 cells	• ↓ T_H1-cell differentiation • ↓ Cell-mediated immunity & APC activity • ↑ B-cell function
IL-12	Macrophages	• ↑ T_H1-cell differentiation • ↑ NK-cell & CD8+ T-cell activity
IFN-gamma	T_H1 cells	• ↑ Intracellular killing by macrophages • ↑ MHC class I & II expression

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Immunology
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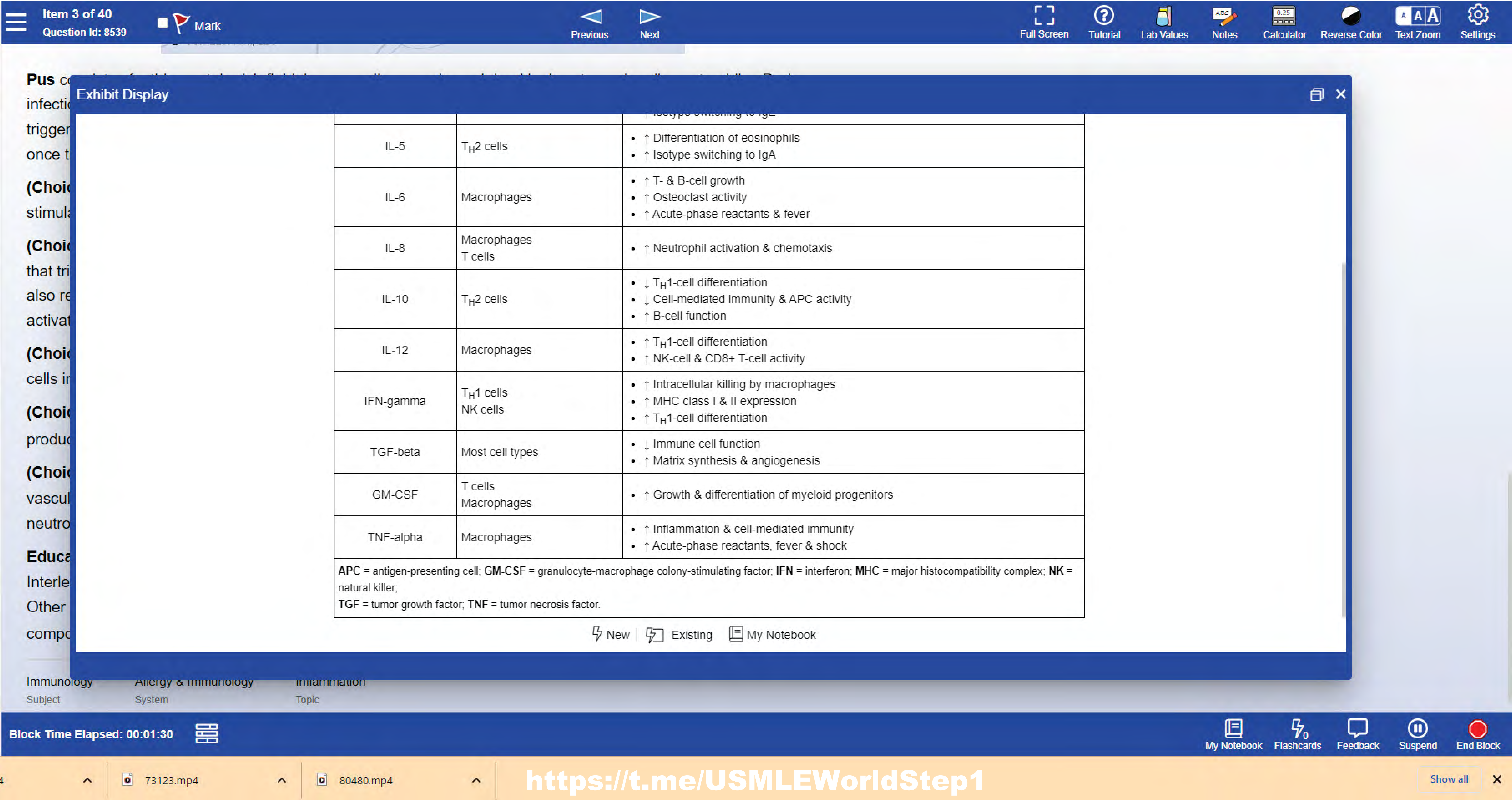
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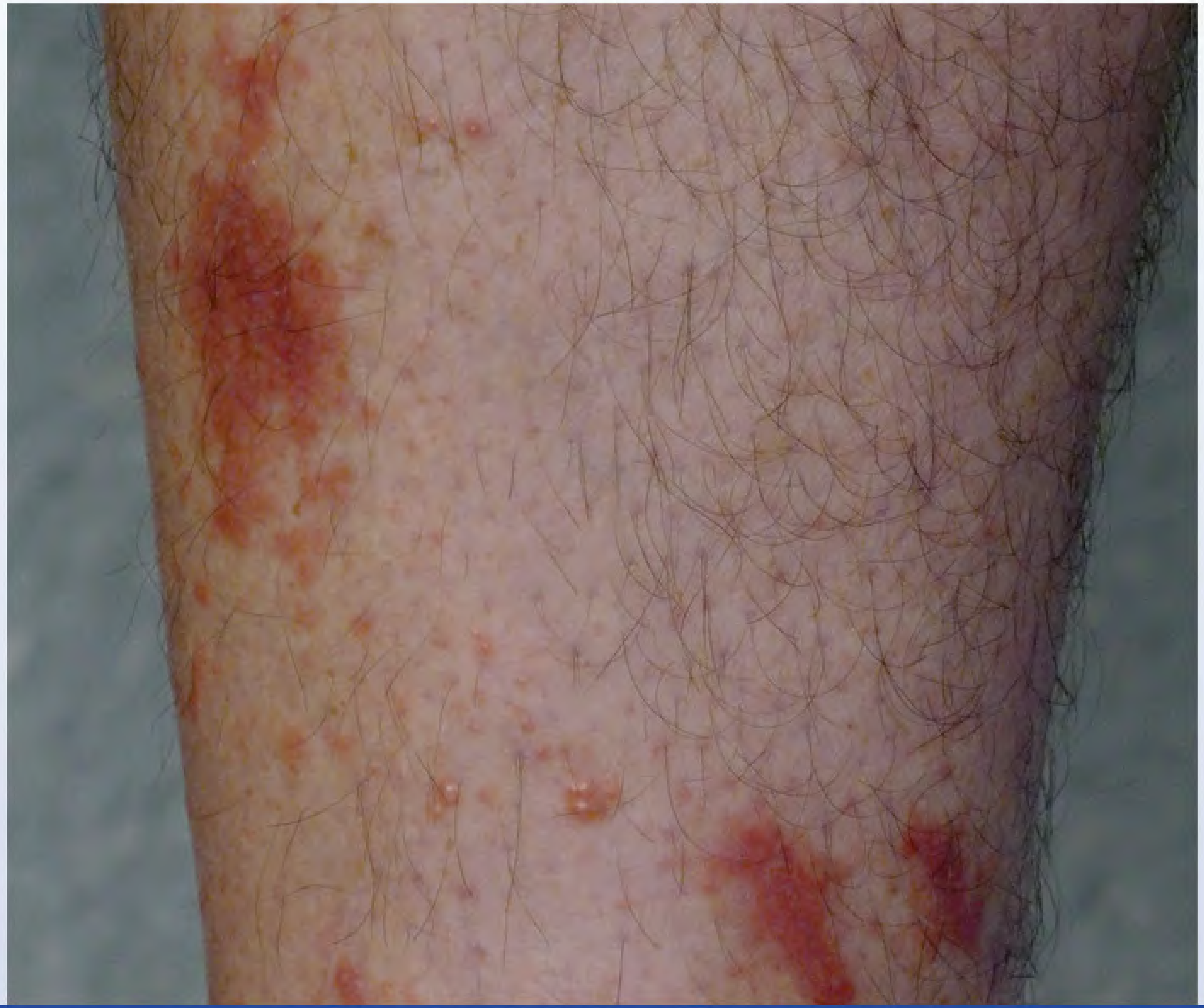
		↑ Isotype switching to IgE
IL-5	T_H2 cells	• ↑ Differentiation of eosinophils • ↑ Isotype switching to IgA
IL-6	Macrophages	• ↑ T- & B-cell growth • ↑ Osteoclast activity • ↑ Acute-phase reactants & fever
IL-8	Macrophages T cells	• ↑ Neutrophil activation & chemotaxis
IL-10	T_H2 cells	• ↓ T_H1-cell differentiation • ↓ Cell-mediated immunity & APC activity • ↑ B-cell function
IL-12	Macrophages	• ↑ T_H1-cell differentiation • ↑ NK-cell & CD8+ T-cell activity
IFN-gamma	T_H1 cells NK cells	• ↑ Intracellular killing by macrophages • ↑ MHC class I & II expression • ↑ T_H1-cell differentiation
TGF-beta	Most cell types	• ↓ Immune cell function • ↑ Matrix synthesis & angiogenesis
GM-CSF	T cells Macrophages	• ↑ Growth & differentiation of myeloid progenitors
TNF-alpha	Macrophages	• ↑ Inflammation & cell-mediated immunity • ↑ Acute-phase reactants, fever & shock

APC = antigen-presenting cell; **GM-CSF** = granulocyte-macrophage colony-stimulating factor; **IFN** = interferon; **MHC** = major histocompatibility complex; **NK** = natural killer;
TGF = tumor growth factor; **TNF** = tumor necrosis factor.

A 34-year-old electric company worker comes to the physician with a skin rash on his right leg. He has not eaten any new foods or changed detergents, soaps, or lotions. On further questioning, the patient recalls that he recently worked on a repair job in an unmaintained, wooded area. He had atopic dermatitis as a child but no other significant illnesses. On physical examination, he appears uncomfortable and is constantly scratching his leg. His lungs are clear bilaterally and his heart sounds are normal. Examination of his right leg shows the findings in the image below.



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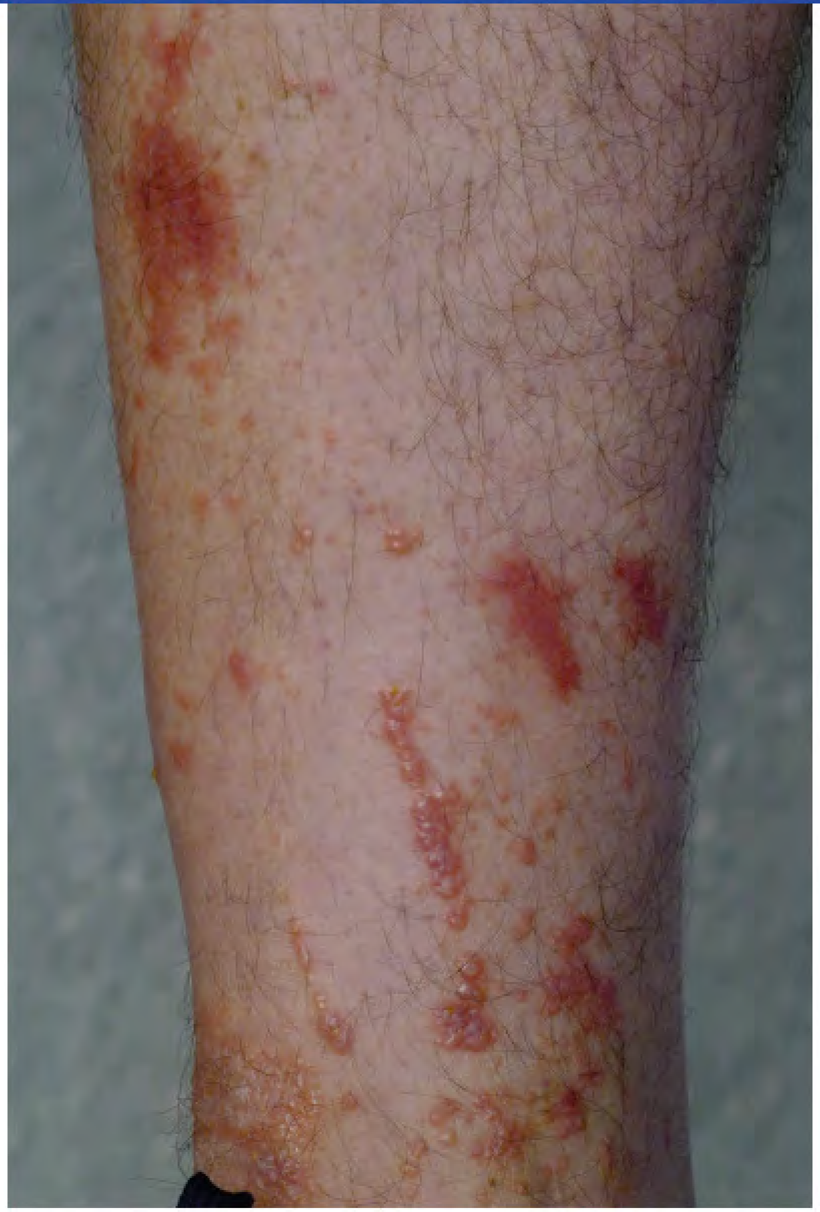

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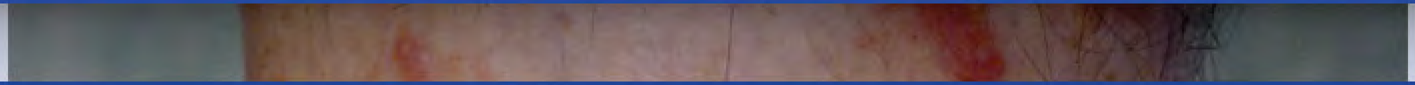

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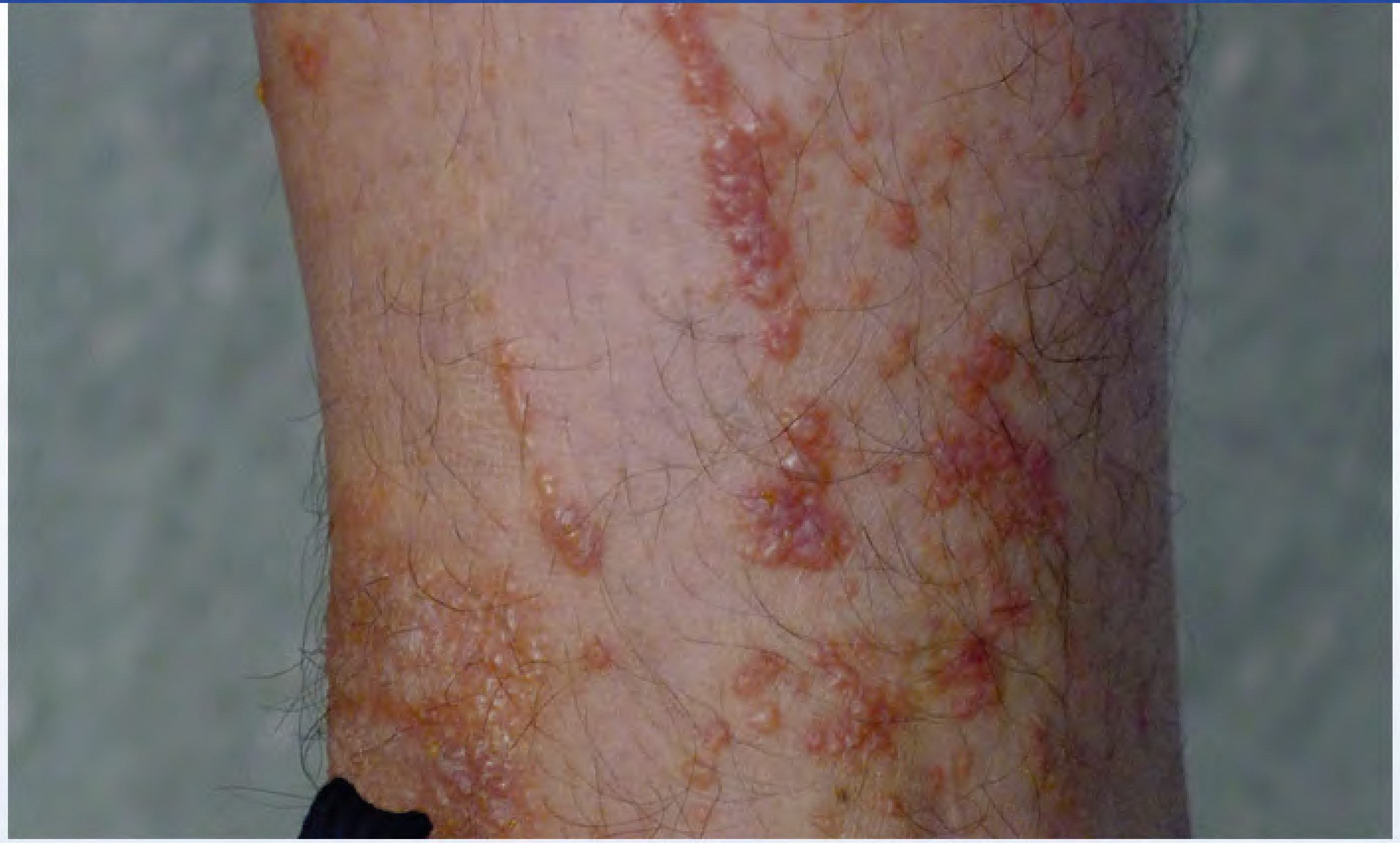

Which of the following cells is most responsible for causing the tissue damage seen in this patient?

○ A. Basophils
○ B. Eosinophils
○ C. Mast cells
○ D. Neutrophils
○ E. Plasma cells
○ F. T lymphocytes

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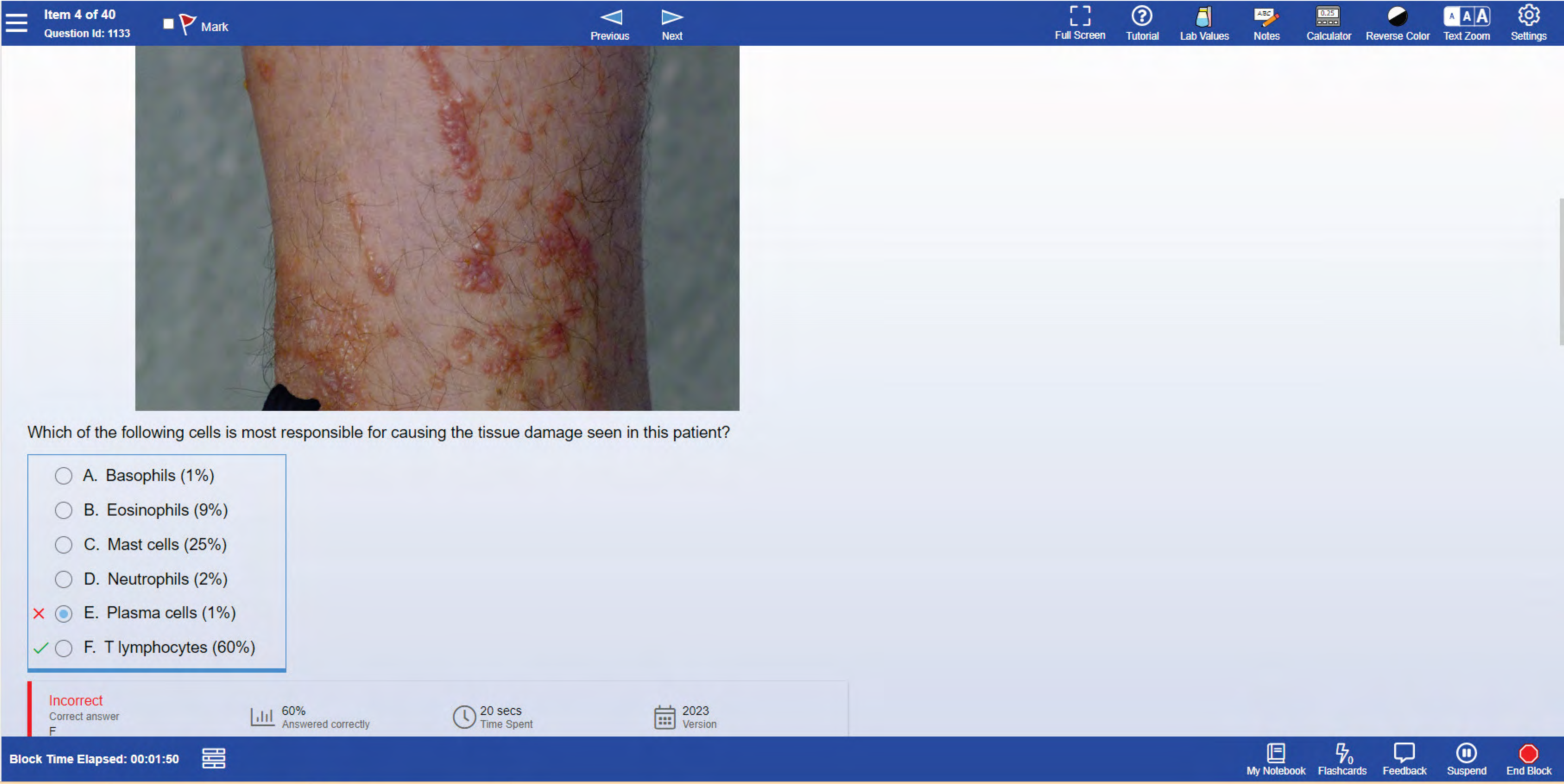
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Which of the following cells is most responsible for causing the tissue damage seen in this patient?

- ○ A. Basophils (1%)
- ○ B. Eosinophils (9%)
- ○ C. Mast cells (25%)
- ○ D. Neutrophils (2%)
- ✗ ● E. Plasma cells (1%)
- ✓ ○ F. T lymphocytes (60%)

Incorrect
Correct answer
F

60%
Answered correctly

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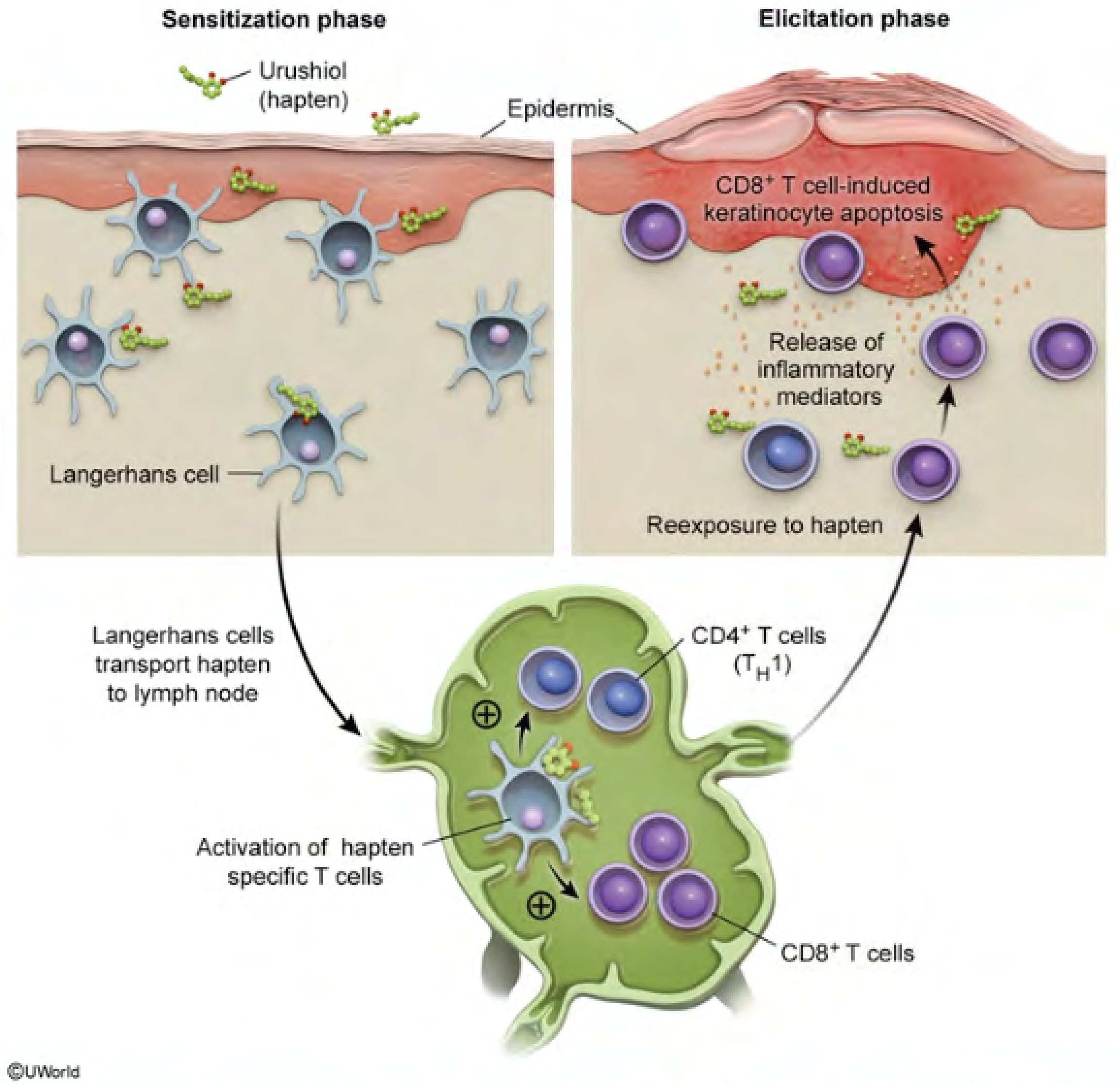
Urushiol-induced contact dermatitis

Exhibit Display

Urushiol-induced contact dermatitis


Sensitization phase
Elicitation phase
Urushiol (hapten)
Epidermis
Langerhans cell
CD8⁺ T cell-induced keratinocyte apoptosis
Release of inflammatory mediators
Reexposure to hapten
Langerhans cells transport hapten to lymph node
CD4⁺ T cells (T_H1)
Activation of hapten specific T cells
CD8⁺ T cells
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This patient's pruritic skin rash following wilderness exposure is consistent with **poison ivy dermatitis**, a form of contact dermatitis. Poison ivy, poison oak, and poison sumac all produce **urushiol**, a small allergenic substance

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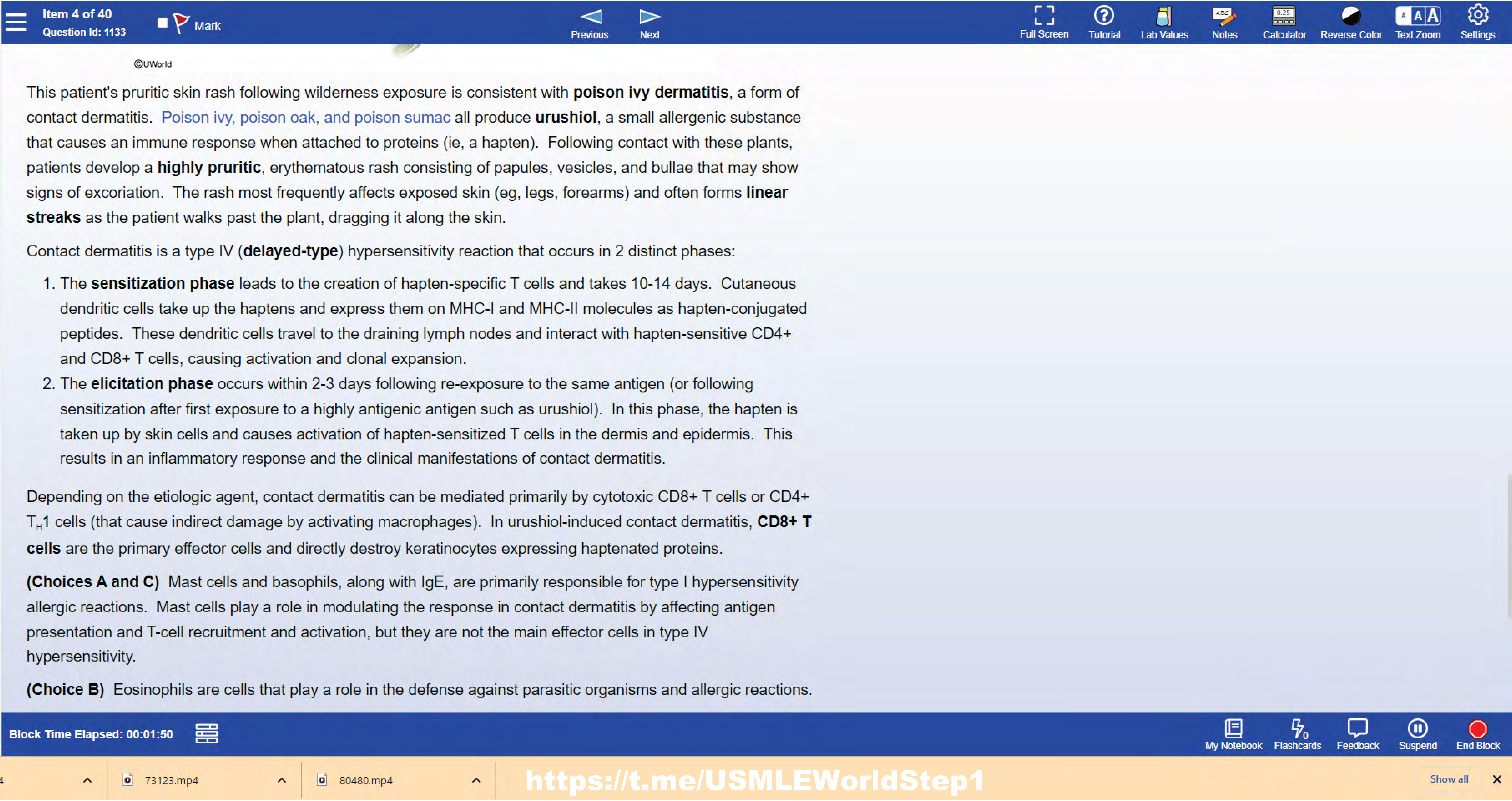


This patient's pruritic skin rash following wilderness exposure is consistent with **poison ivy dermatitis**, a form of contact dermatitis. Poison ivy, poison oak, and poison sumac all produce **urushiol**, a small allergenic substance that causes an immune response when attached to proteins (ie, a hapten). Following contact with these plants, patients develop a **highly pruritic**, erythematous rash consisting of papules, vesicles, and bullae that may show signs of excoriation. The rash most frequently affects exposed skin (eg, legs, forearms) and often forms **linear streaks** as the patient walks past the plant, dragging it along the skin.

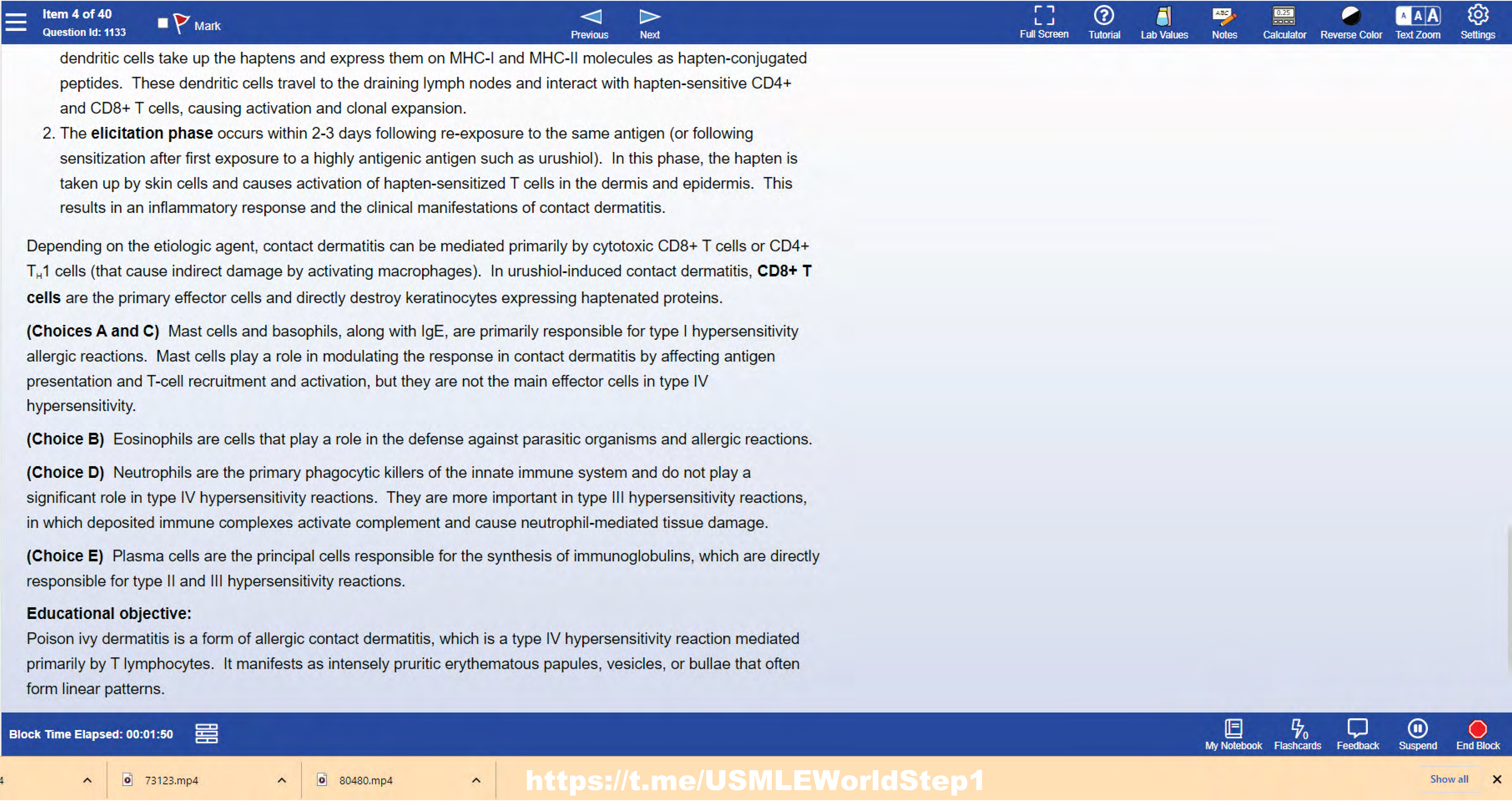
Contact dermatitis is a type IV (**delayed-type**) hypersensitivity reaction that occurs in 2 distinct phases:

1. The **sensitization phase** leads to the creation of hapten-specific T cells and takes 10-14 days. Cutaneous dendritic cells take up the haptens and express them on MHC-I and MHC-II molecules as hapten-conjugated peptides. These dendritic cells travel to the draining lymph nodes and interact with hapten-sensitive CD4+ and CD8+ T cells, causing activation and clonal expansion.
2. The **elicitation phase** occurs within 2-3 days following re-exposure to the same antigen (or following sensitization after first exposure to a highly antigenic antigen such as urushiol). In this phase, the hapten is taken up by skin cells and causes activation of hapten-sensitized T cells in the dermis and epidermis. This results in an inflammatory response and the clinical manifestations of contact dermatitis.

Depending on the etiologic agent, contact dermatitis can be mediated primarily by cytotoxic CD8+ T cells or CD4+ T_H1 cells (that cause indirect damage by activating macrophages). In urushiol-induced contact dermatitis, **CD8+ T cells** are the primary effector cells and directly destroy keratinocytes expressing haptenated proteins.

(Choices A and C) Mast cells and basophils, along with IgE, are primarily responsible for type I hypersensitivity allergic reactions. Mast cells play a role in modulating the response in contact dermatitis by affecting antigen presentation and T-cell recruitment and activation, but they are not the main effector cells in type IV hypersensitivity.

(Choice B) Eosinophils are cells that play a role in the defense against parasitic organisms and allergic reactions.



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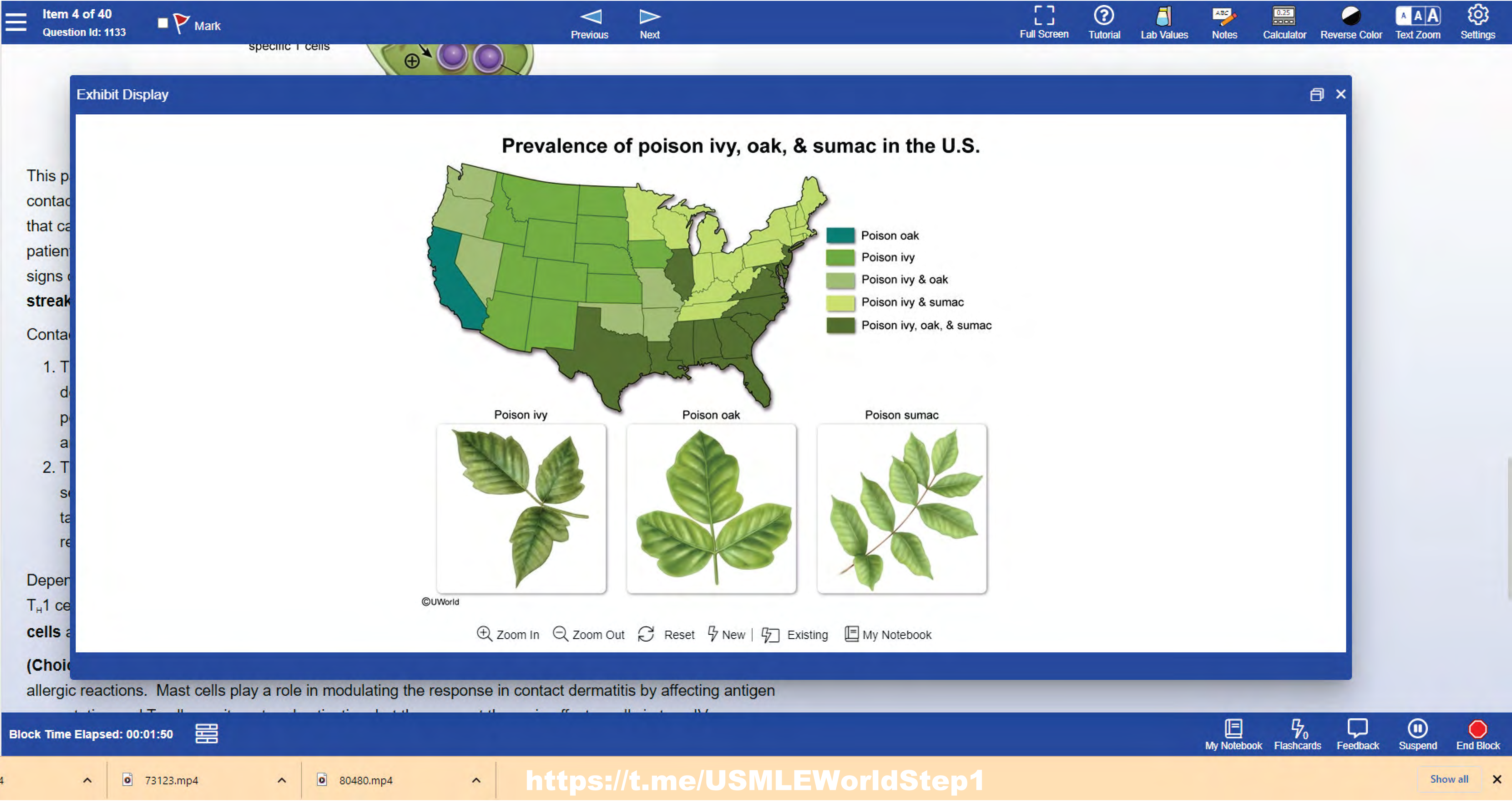
(Choice B) Eosinophils are cells that play a role in the defense against parasitic organisms and allergic reactions.

(Choice D) Neutrophils are the primary phagocytic killers of the innate immune system and do not play a significant role in type IV hypersensitivity reactions. They are more important in type III hypersensitivity reactions, in which deposited immune complexes activate complement and cause neutrophil-mediated tissue damage.

(Choice E) Plasma cells are the principal cells responsible for the synthesis of immunoglobulins, which are directly responsible for type II and III hypersensitivity reactions.

Educational objective:

Poison ivy dermatitis is a form of allergic contact dermatitis, which is a type IV hypersensitivity reaction mediated primarily by T lymphocytes. It manifests as intensely pruritic erythematous papules, vesicles, or bullae that often form linear patterns.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Prevalence of poison ivy, oak, & sumac in the U.S.
Poison oak
Poison ivy
Poison ivy & oak
Poison ivy & sumac
Poison ivy, oak, & sumac
Poison ivy
Poison oak
Poison sumac
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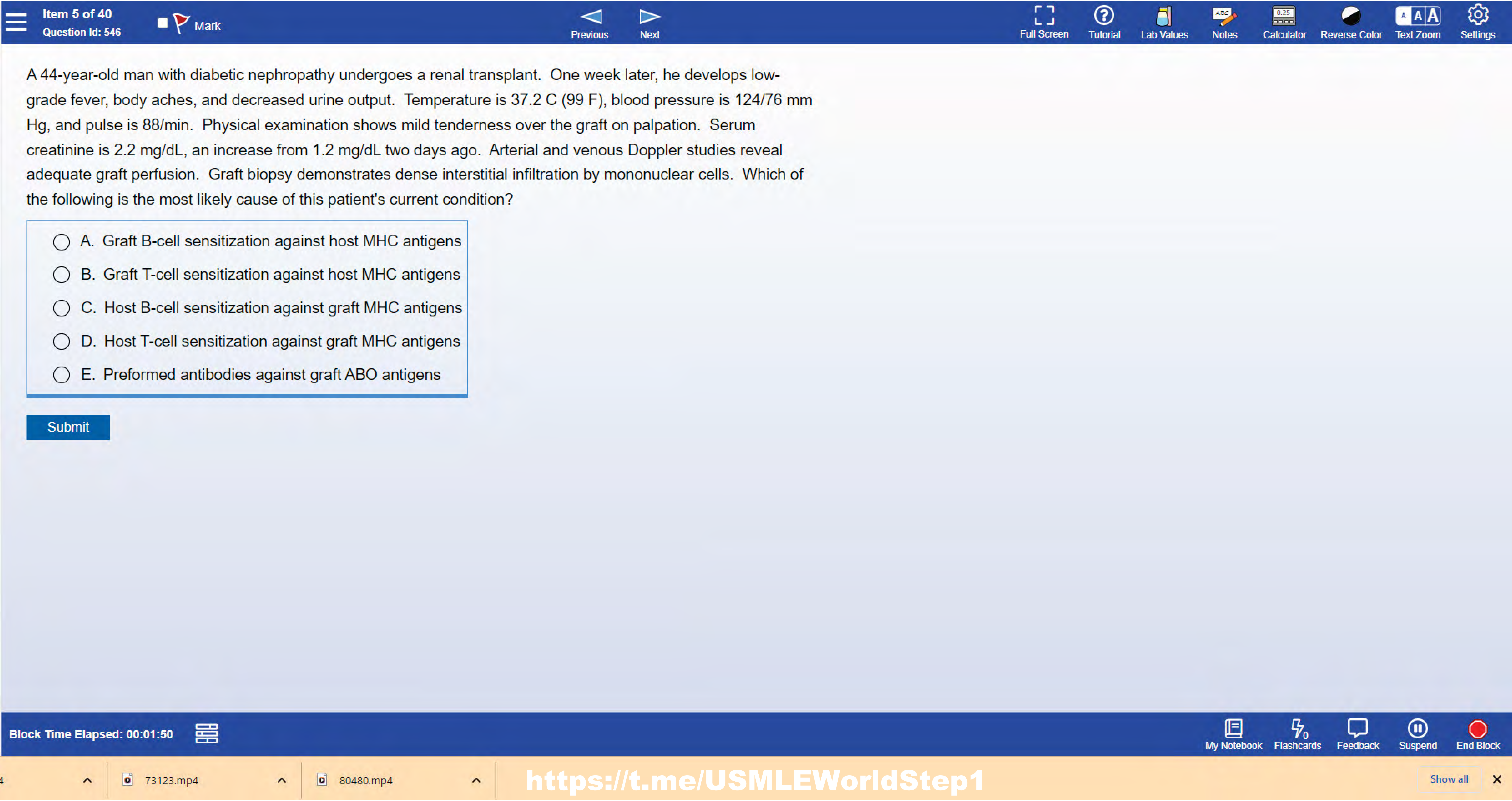
allergic reactions. Mast cells play a role in modulating the response in contact dermatitis by affecting antigen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A 44-year-old man with diabetic nephropathy undergoes a renal transplant. One week later, he develops low-grade fever, body aches, and decreased urine output. Temperature is 37.2 C (99 F), blood pressure is 124/76 mm Hg, and pulse is 88/min. Physical examination shows mild tenderness over the graft on palpation. Serum creatinine is 2.2 mg/dL, an increase from 1.2 mg/dL two days ago. Arterial and venous Doppler studies reveal adequate graft perfusion. Graft biopsy demonstrates dense interstitial infiltration by mononuclear cells. Which of the following is the most likely cause of this patient's current condition?

○ A. Graft B-cell sensitization against host MHC antigens
○ B. Graft T-cell sensitization against host MHC antigens
○ C. Host B-cell sensitization against graft MHC antigens
○ D. Host T-cell sensitization against graft MHC antigens
○ E. Preformed antibodies against graft ABO antigens

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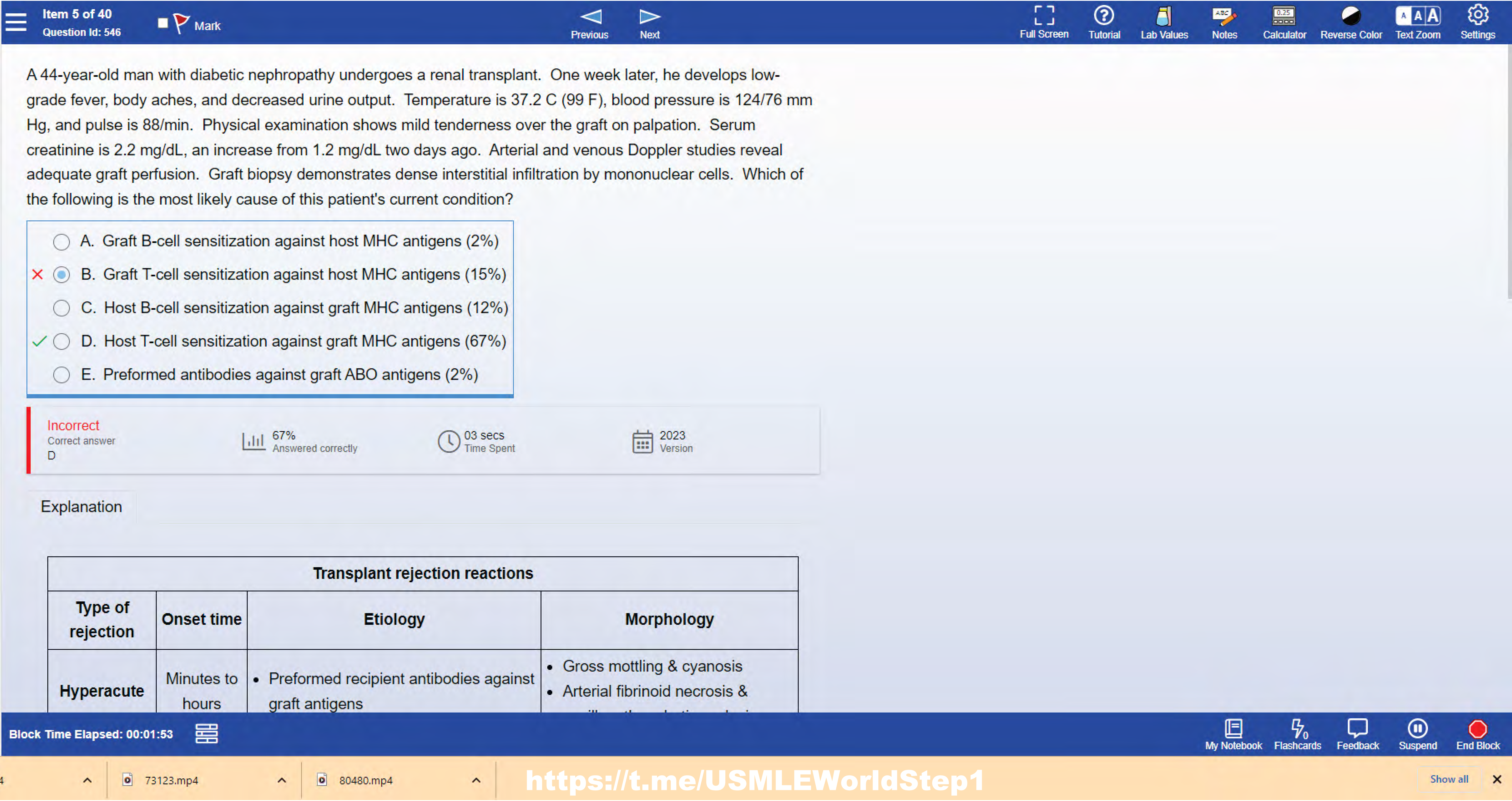
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- ○ A. Graft B-cell sensitization against host MHC antigens (2%)
- ✗ ● B. Graft T-cell sensitization against host MHC antigens (15%)
- ○ C. Host B-cell sensitization against graft MHC antigens (12%)
- ✓ ○ D. Host T-cell sensitization against graft MHC antigens (67%)
- ○ E. Preformed antibodies against graft ABO antigens (2%)

Incorrect
Correct answer
D

67%
Answered correctly

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Explanation

Transplant rejection reactions			
Type of rejection	**Onset time**	**Etiology**	**Morphology**
Hyperacute	Minutes to hours	• Preformed recipient antibodies against graft antigens	• Gross mottling & cyanosis • Arterial fibrinoid necrosis &

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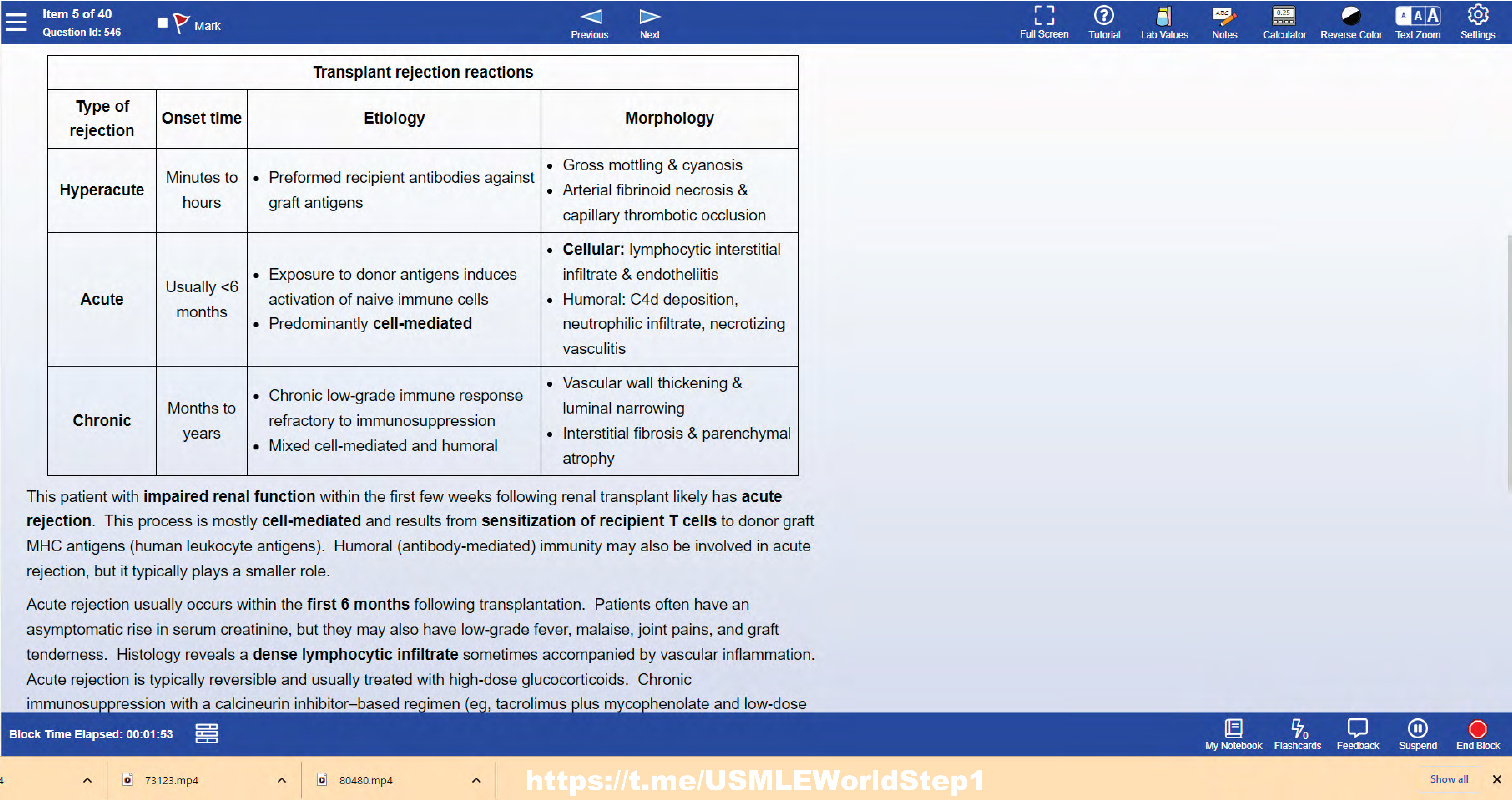
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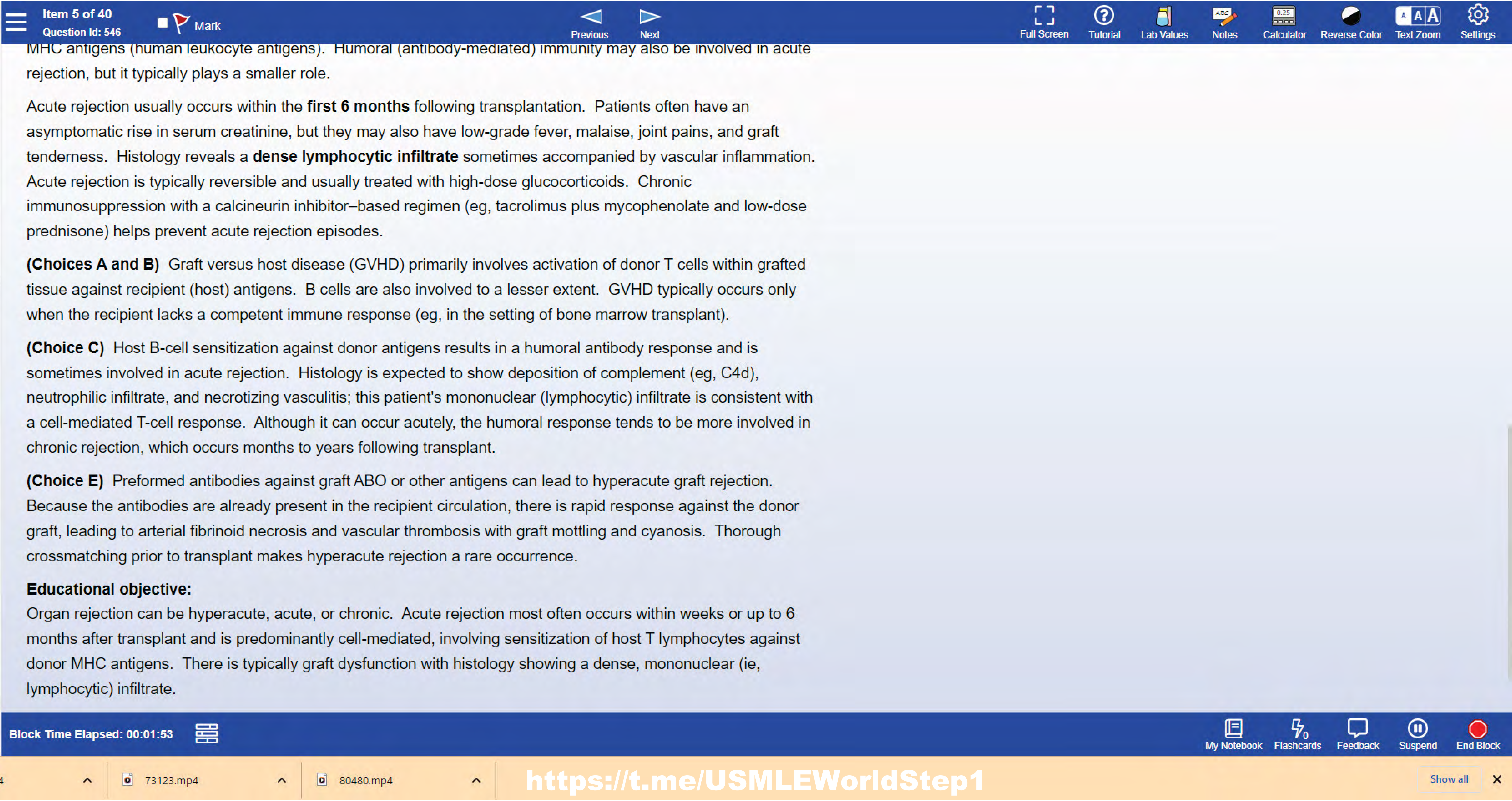
Transplant rejection reactions

Type of rejection	Onset time	Etiology	Morphology
Hyperacute	Minutes to hours	• Preformed recipient antibodies against graft antigens	• Gross mottling & cyanosis • Arterial fibrinoid necrosis & capillary thrombotic occlusion
Acute	Usually <6 months	• Exposure to donor antigens induces activation of naive immune cells • Predominantly **cell-mediated**	• **Cellular:** lymphocytic interstitial infiltrate & endotheliitis • Humoral: C4d deposition, neutrophilic infiltrate, necrotizing vasculitis
Chronic	Months to years	• Chronic low-grade immune response refractory to immunosuppression • Mixed cell-mediated and humoral	• Vascular wall thickening & luminal narrowing • Interstitial fibrosis & parenchymal atrophy

This patient with **impaired renal function** within the first few weeks following renal transplant likely has **acute rejection**. This process is mostly **cell-mediated** and results from **sensitization of recipient T cells** to donor graft MHC antigens (human leukocyte antigens). Humoral (antibody-mediated) immunity may also be involved in acute rejection, but it typically plays a smaller role.

Acute rejection usually occurs within the **first 6 months** following transplantation. Patients often have an asymptomatic rise in serum creatinine, but they may also have low-grade fever, malaise, joint pains, and graft tenderness. Histology reveals a **dense lymphocytic infiltrate** sometimes accompanied by vascular inflammation. Acute rejection is typically reversible and usually treated with high-dose glucocorticoids. Chronic immunosuppression with a calcineurin inhibitor–based regimen (eg, tacrolimus plus mycophenolate and low-dose



MHC antigens (human leukocyte antigens). Humoral (antibody-mediated) immunity may also be involved in acute rejection, but it typically plays a smaller role.

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(Choices A and B) Graft versus host disease (GVHD) primarily involves activation of donor T cells within grafted tissue against recipient (host) antigens. B cells are also involved to a lesser extent. GVHD typically occurs only when the recipient lacks a competent immune response (eg, in the setting of bone marrow transplant).

(Choice C) Host B-cell sensitization against donor antigens results in a humoral antibody response and is sometimes involved in acute rejection. Histology is expected to show deposition of complement (eg, C4d), neutrophilic infiltrate, and necrotizing vasculitis; this patient's mononuclear (lymphocytic) infiltrate is consistent with a cell-mediated T-cell response. Although it can occur acutely, the humoral response tends to be more involved in chronic rejection, which occurs months to years following transplant.

(Choice E) Preformed antibodies against graft ABO or other antigens can lead to hyperacute graft rejection. Because the antibodies are already present in the recipient circulation, there is rapid response against the donor graft, leading to arterial fibrinoid necrosis and vascular thrombosis with graft mottling and cyanosis. Thorough crossmatching prior to transplant makes hyperacute rejection a rare occurrence.

Educational objective:

Organ rejection can be hyperacute, acute, or chronic. Acute rejection most often occurs within weeks or up to 6 months after transplant and is predominantly cell-mediated, involving sensitization of host T lymphocytes against donor MHC antigens. There is typically graft dysfunction with histology showing a dense, mononuclear (ie, lymphocytic) infiltrate.

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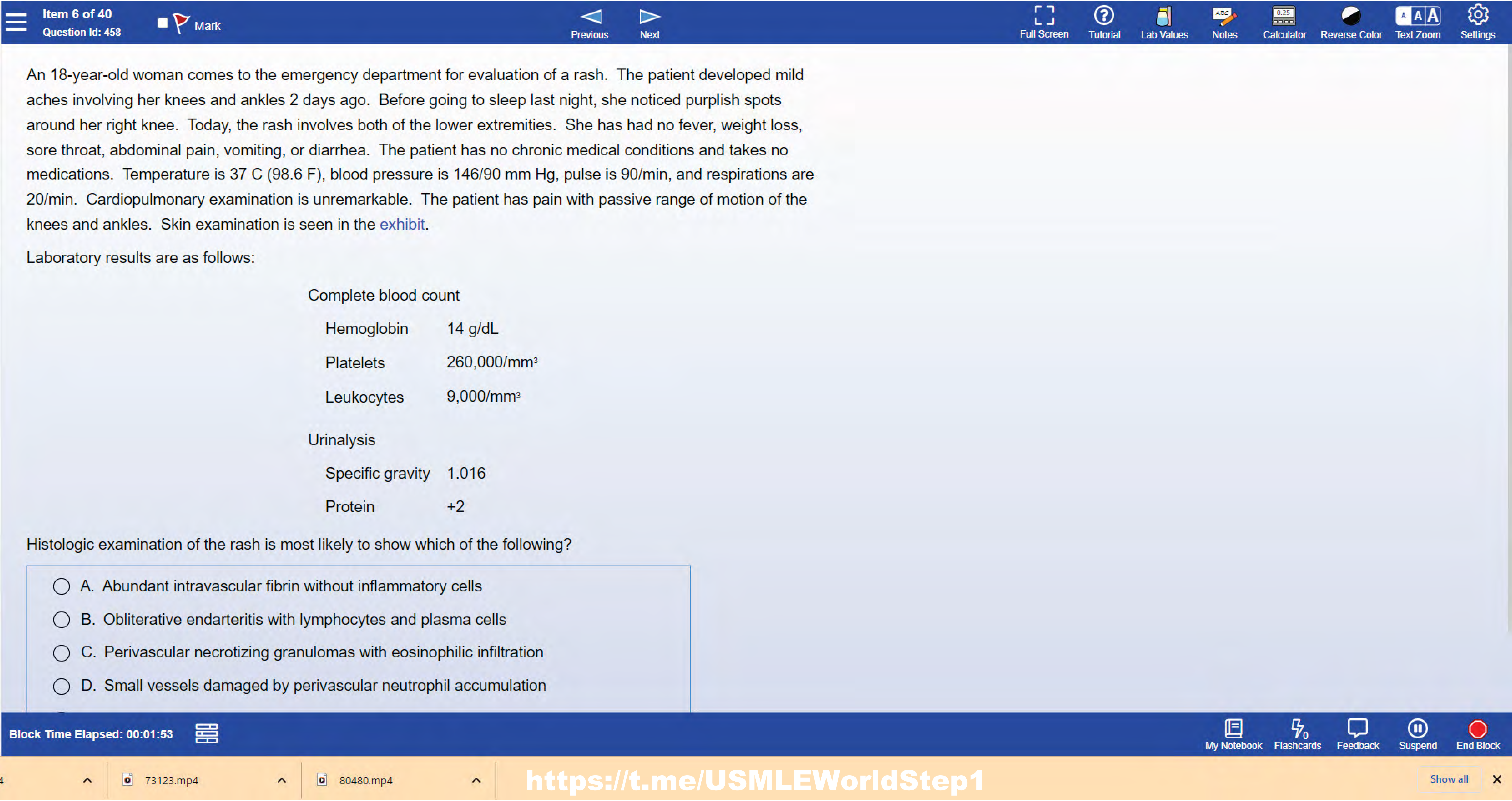
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An 18-year-old woman comes to the emergency department for evaluation of a rash. The patient developed mild aches involving her knees and ankles 2 days ago. Before going to sleep last night, she noticed purplish spots around her right knee. Today, the rash involves both of the lower extremities. She has had no fever, weight loss, sore throat, abdominal pain, vomiting, or diarrhea. The patient has no chronic medical conditions and takes no medications. Temperature is 37 C (98.6 F), blood pressure is 146/90 mm Hg, pulse is 90/min, and respirations are 20/min. Cardiopulmonary examination is unremarkable. The patient has pain with passive range of motion of the knees and ankles. Skin examination is seen in the exhibit.

Laboratory results are as follows:

Complete blood count	
Hemoglobin	14 g/dL
Platelets	260,000/mm^3
Leukocytes	9,000/mm^3
Urinalysis	
Specific gravity	1.016
Protein	+2

Histologic examination of the rash is most likely to show which of the following?

○ A. Abundant intravascular fibrin without inflammatory cells

○ B. Obliterative endarteritis with lymphocytes and plasma cells

○ C. Perivascular necrotizing granulomas with eosinophilic infiltration

○ D. Small vessels damaged by perivascular neutrophil accumulation

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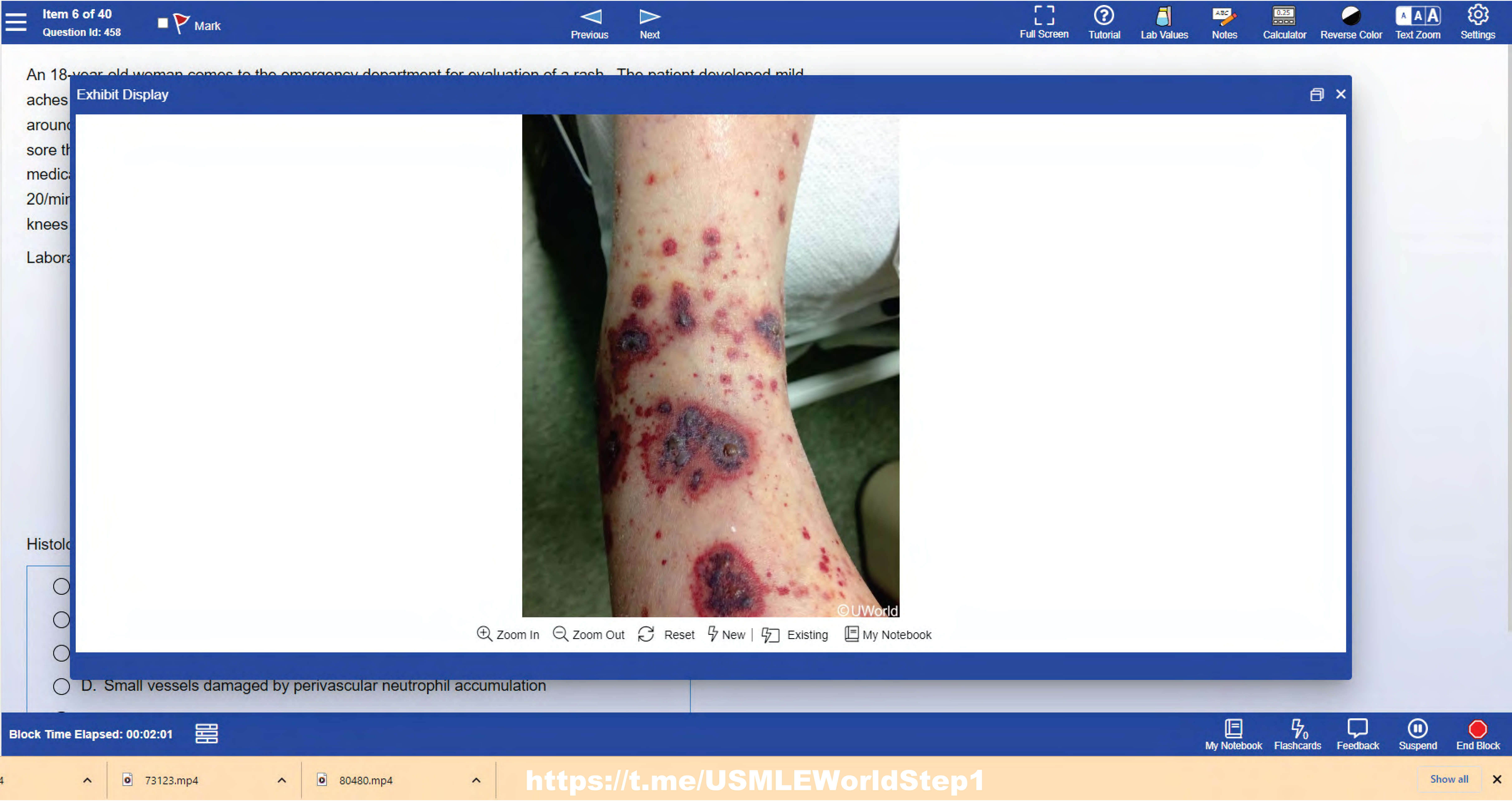
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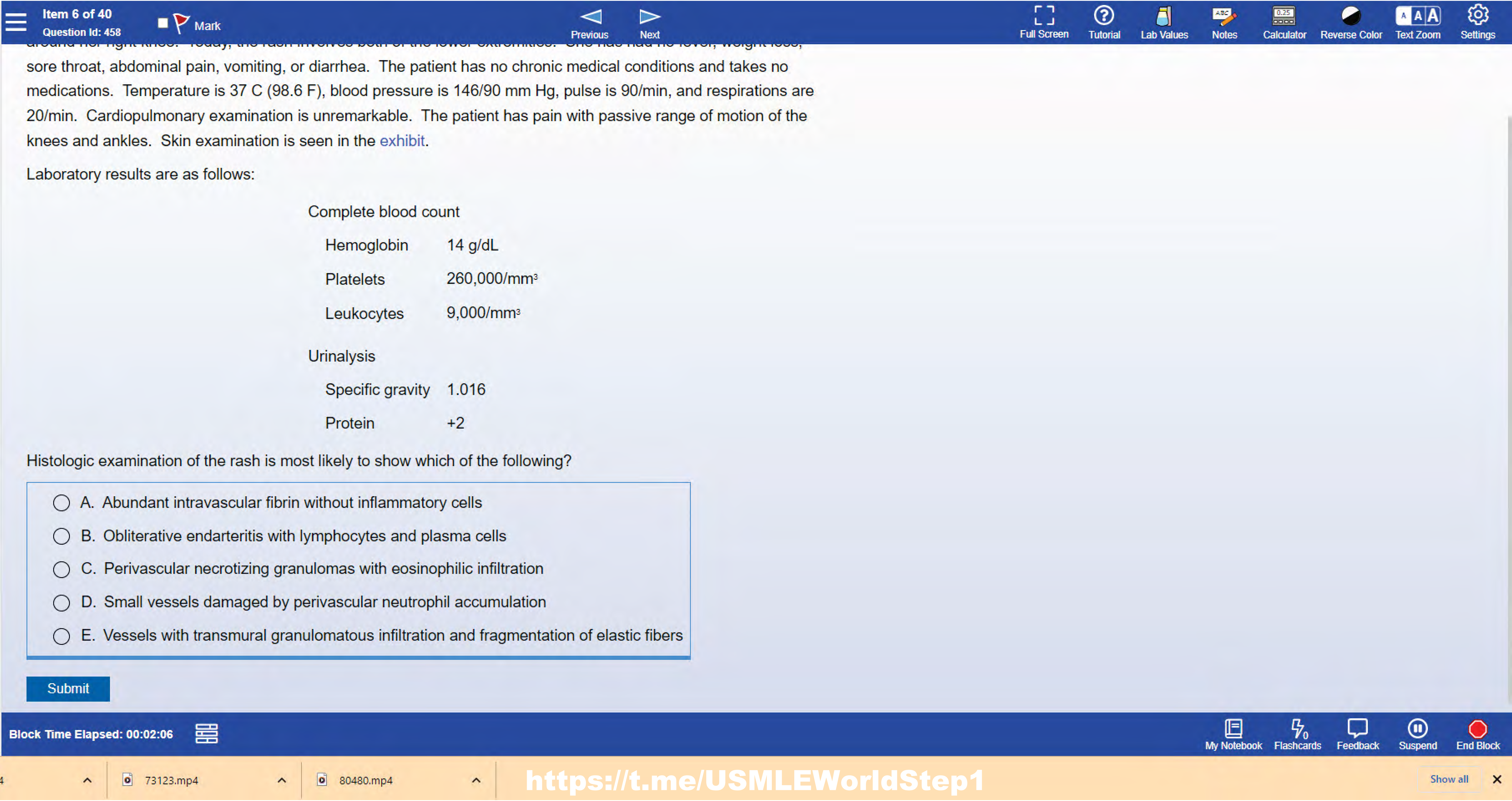
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○ A. Abundant intravascular fibrin without inflammatory cells
○ B. Obliterative endarteritis with lymphocytes and plasma cells
○ C. Perivascular necrotizing granulomas with eosinophilic infiltration
○ D. Small vessels damaged by perivascular neutrophil accumulation
○ E. Vessels with transmural granulomatous infiltration and fragmentation of elastic fibers

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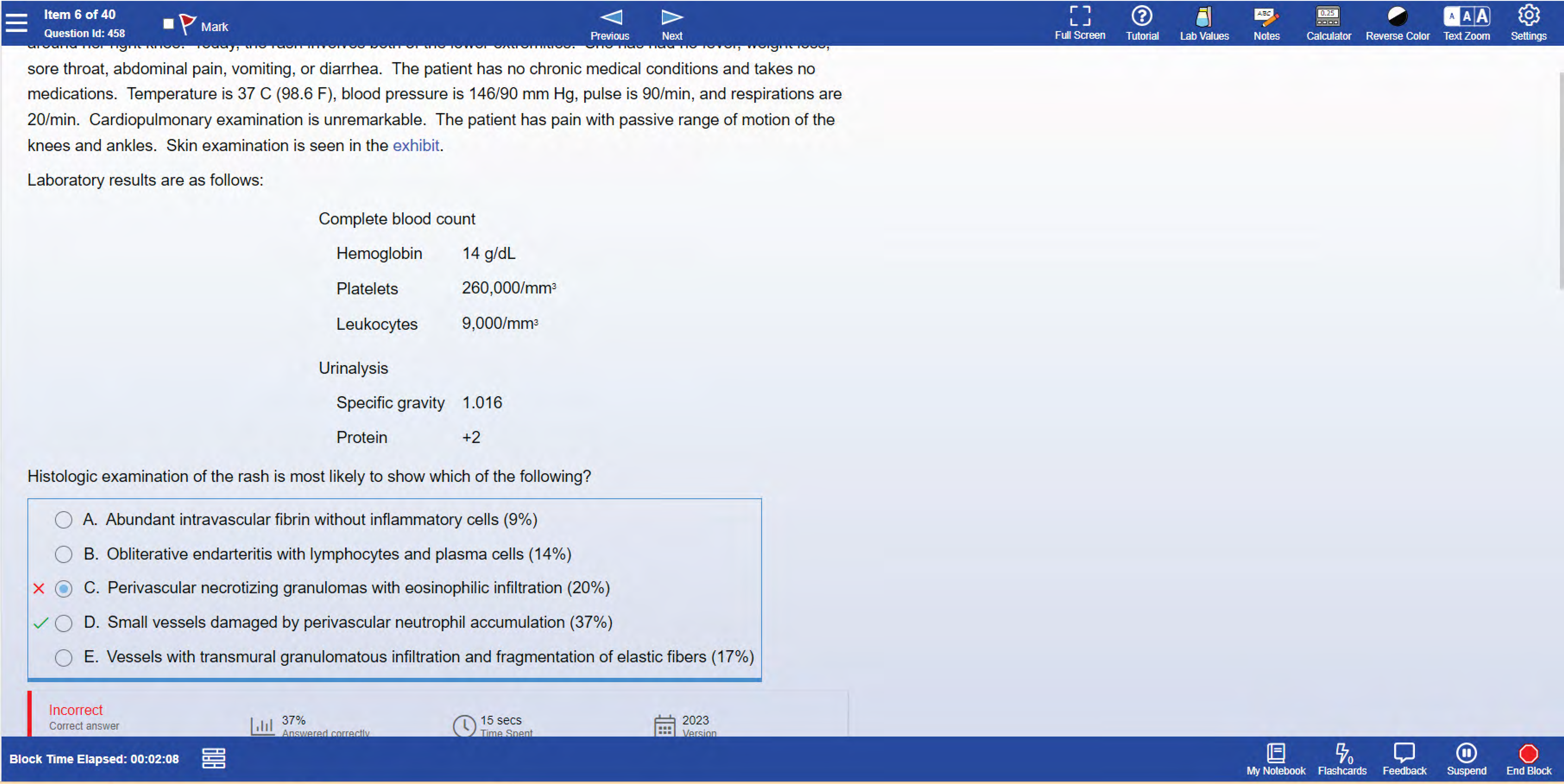
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Leukocytes	9,000/mm^3
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Protein	+2

Histologic examination of the rash is most likely to show which of the following?

○ A. Abundant intravascular fibrin without inflammatory cells (9%)
○ B. Obliterative endarteritis with lymphocytes and plasma cells (14%)
✗ ● C. Perivascular necrotizing granulomas with eosinophilic infiltration (20%)
✓ ○ D. Small vessels damaged by perivascular neutrophil accumulation (37%)
○ E. Vessels with transmural granulomatous infiltration and fragmentation of elastic fibers (17%)

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Correct answer

37%
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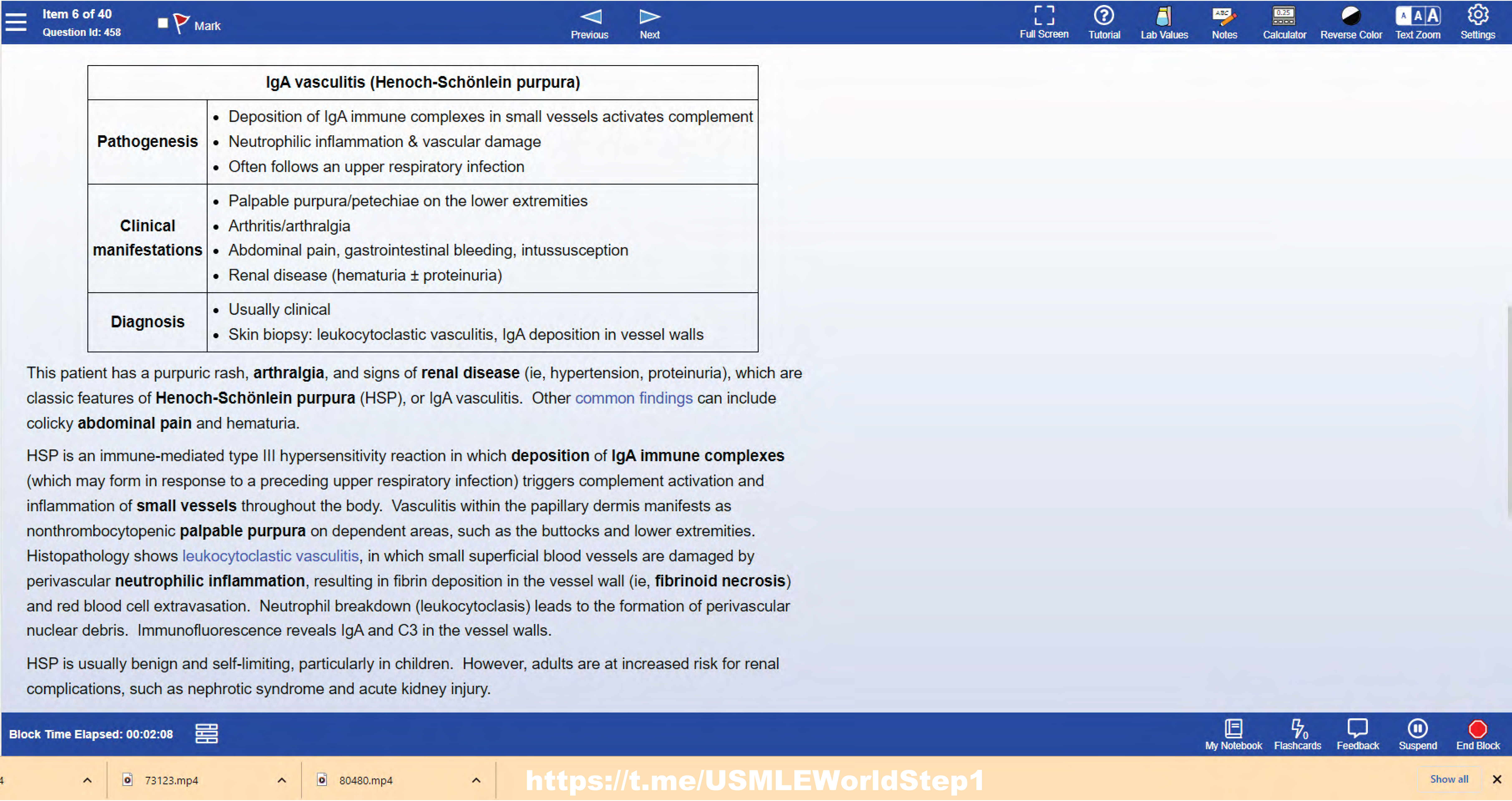
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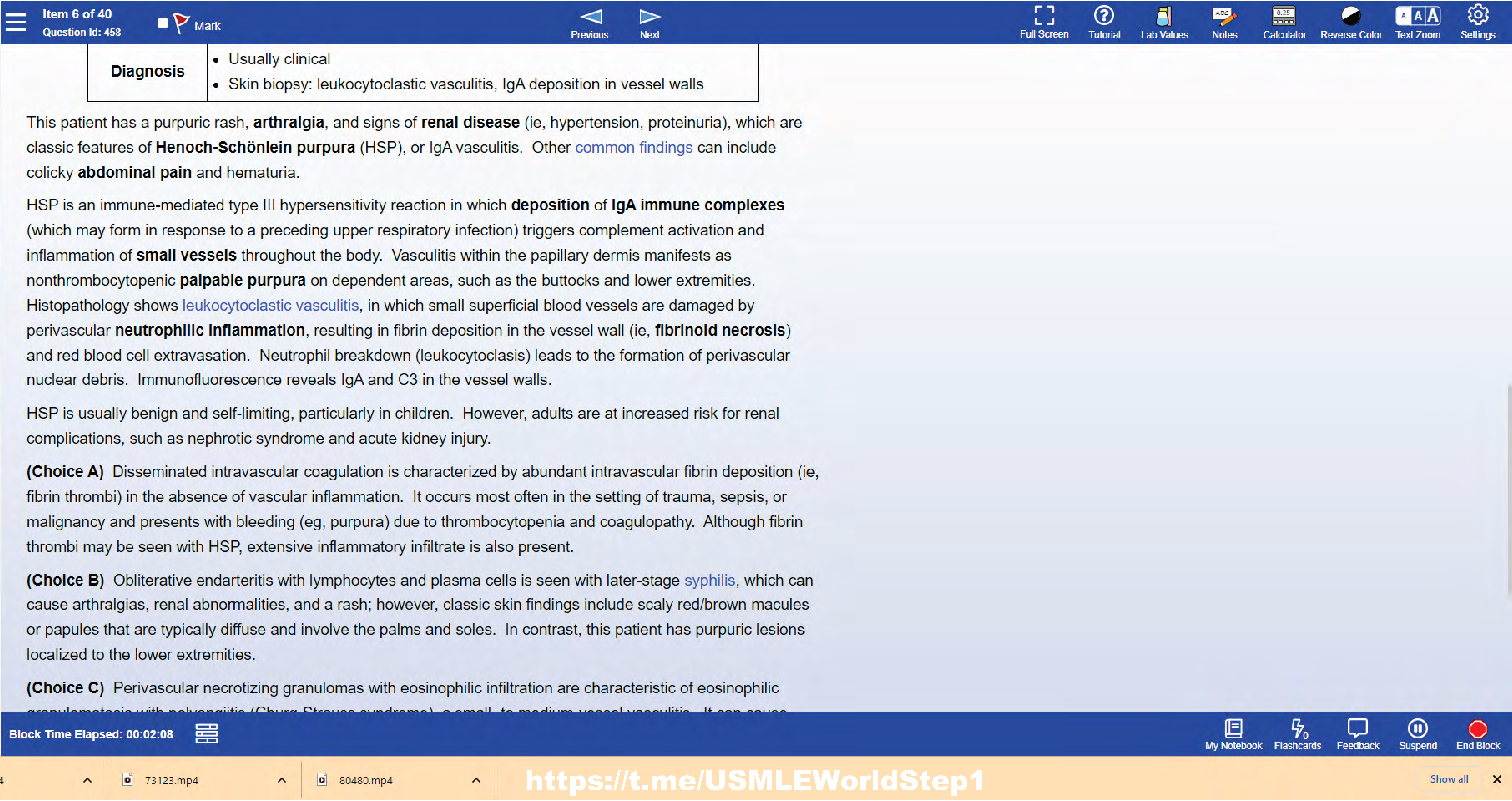
IgA vasculitis (Henoch-Schönlein purpura)	
Pathogenesis	• Deposition of IgA immune complexes in small vessels activates complement • Neutrophilic inflammation & vascular damage • Often follows an upper respiratory infection
Clinical manifestations	• Palpable purpura/petechiae on the lower extremities • Arthritis/arthralgia • Abdominal pain, gastrointestinal bleeding, intussusception • Renal disease (hematuria ± proteinuria)
Diagnosis	• Usually clinical • Skin biopsy: leukocytoclastic vasculitis, IgA deposition in vessel walls

This patient has a purpuric rash, **arthralgia**, and signs of **renal disease** (ie, hypertension, proteinuria), which are classic features of **Henoch-Schönlein purpura** (HSP), or IgA vasculitis. Other common findings can include colicky **abdominal pain** and hematuria.

HSP is an immune-mediated type III hypersensitivity reaction in which **deposition** of **IgA immune complexes** (which may form in response to a preceding upper respiratory infection) triggers complement activation and inflammation of **small vessels** throughout the body. Vasculitis within the papillary dermis manifests as nonthrombocytopenic **palpable purpura** on dependent areas, such as the buttocks and lower extremities. Histopathology shows leukocytoclastic vasculitis, in which small superficial blood vessels are damaged by perivascular **neutrophilic inflammation**, resulting in fibrin deposition in the vessel wall (ie, **fibrinoid necrosis**) and red blood cell extravasation. Neutrophil breakdown (leukocytoclasis) leads to the formation of perivascular nuclear debris. Immunofluorescence reveals IgA and C3 in the vessel walls.

HSP is usually benign and self-limiting, particularly in children. However, adults are at increased risk for renal complications, such as nephrotic syndrome and acute kidney injury.



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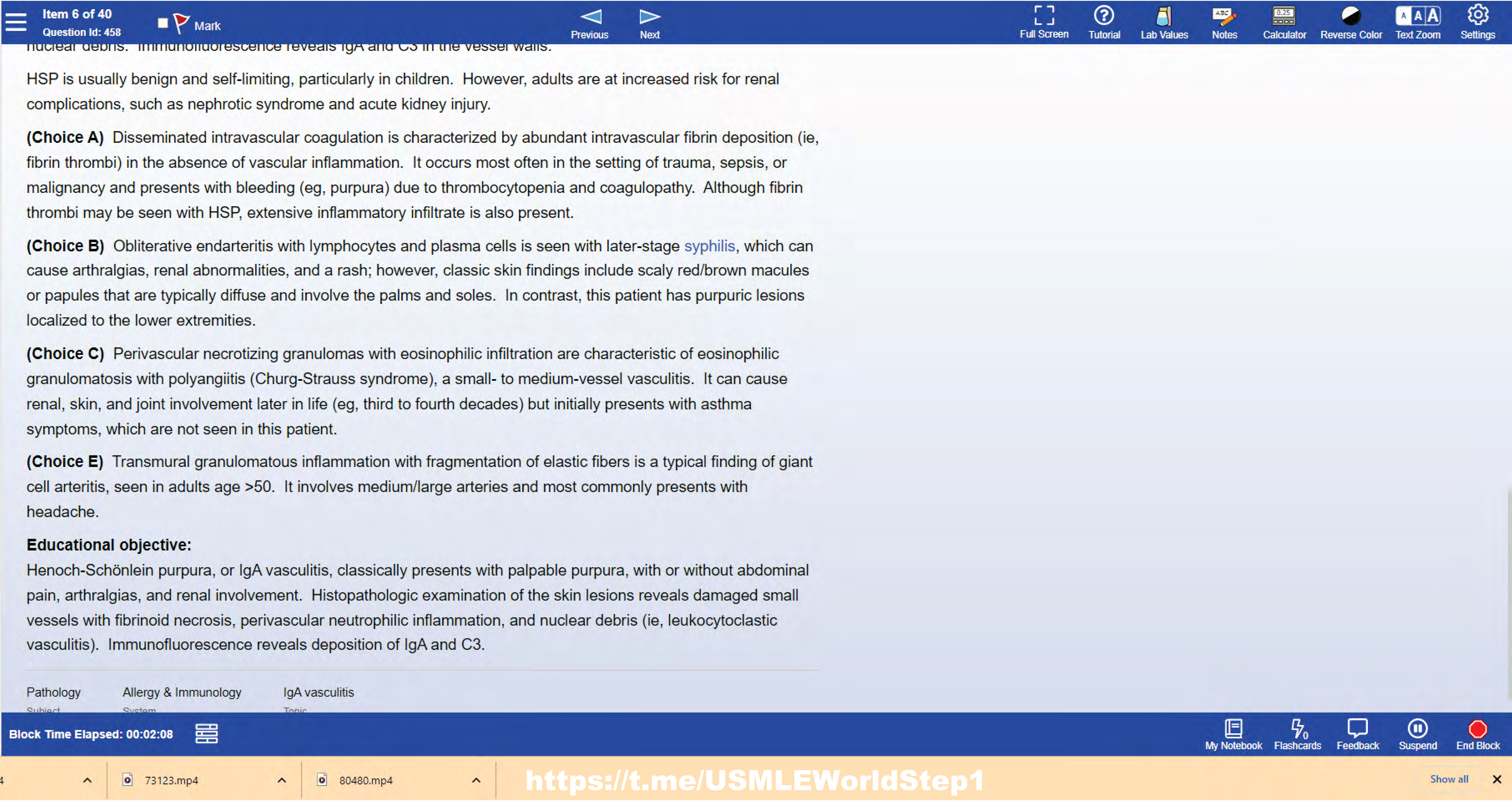
(Choice A) Disseminated intravascular coagulation is characterized by abundant intravascular fibrin deposition (ie, fibrin thrombi) in the absence of vascular inflammation. It occurs most often in the setting of trauma, sepsis, or malignancy and presents with bleeding (eg, purpura) due to thrombocytopenia and coagulopathy. Although fibrin thrombi may be seen with HSP, extensive inflammatory infiltrate is also present.

(Choice B) Obliterative endarteritis with lymphocytes and plasma cells is seen with later-stage syphilis, which can cause arthralgias, renal abnormalities, and a rash; however, classic skin findings include scaly red/brown macules or papules that are typically diffuse and involve the palms and soles. In contrast, this patient has purpuric lesions localized to the lower extremities.

(Choice C) Perivascular necrotizing granulomas with eosinophilic infiltration are characteristic of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), a small- to medium-vessel vasculitis. It can cause



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(Choice A) Disseminated intravascular coagulation is characterized by abundant intravascular fibrin deposition (ie, fibrin thrombi) in the absence of vascular inflammation. It occurs most often in the setting of trauma, sepsis, or malignancy and presents with bleeding (eg, purpura) due to thrombocytopenia and coagulopathy. Although fibrin thrombi may be seen with HSP, extensive inflammatory infiltrate is also present.

(Choice B) Obliterative endarteritis with lymphocytes and plasma cells is seen with later-stage syphilis, which can cause arthralgias, renal abnormalities, and a rash; however, classic skin findings include scaly red/brown macules or papules that are typically diffuse and involve the palms and soles. In contrast, this patient has purpuric lesions localized to the lower extremities.

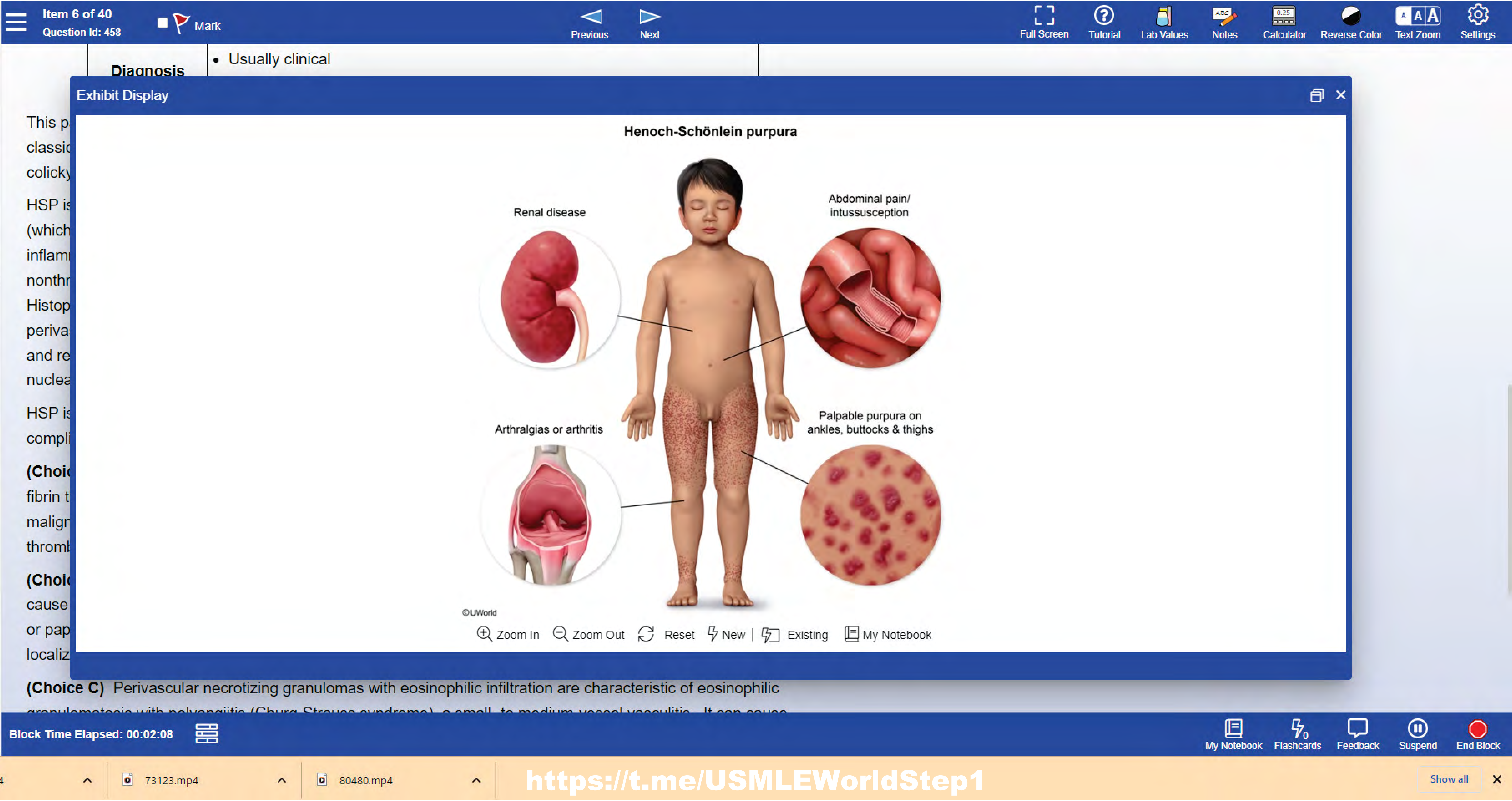
(Choice C) Perivascular necrotizing granulomas with eosinophilic infiltration are characteristic of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), a small- to medium-vessel vasculitis. It can cause renal, skin, and joint involvement later in life (eg, third to fourth decades) but initially presents with asthma symptoms, which are not seen in this patient.

(Choice E) Transmural granulomatous inflammation with fragmentation of elastic fibers is a typical finding of giant cell arteritis, seen in adults age >50. It involves medium/large arteries and most commonly presents with headache.

Educational objective:

Henoch-Schönlein purpura, or IgA vasculitis, classically presents with palpable purpura, with or without abdominal pain, arthralgias, and renal involvement. Histopathologic examination of the skin lesions reveals damaged small vessels with fibrinoid necrosis, perivascular neutrophilic inflammation, and nuclear debris (ie, leukocytoclastic vasculitis). Immunofluorescence reveals deposition of IgA and C3.

Pathology	Allergy & Immunology	IgA vasculitis
Subject	System	Topic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(Choice C) Perivascular necrotizing granulomas with eosinophilic infiltration are characteristic of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), a small- to medium-vessel vasculitis. It can cause

Henoch-Schönlein purpura

Renal disease
Abdominal pain/
intussusception
Arthralgias or arthritis
Palpable purpura on
ankles, buttocks & thighs

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Diagnosis	- Usually clinical

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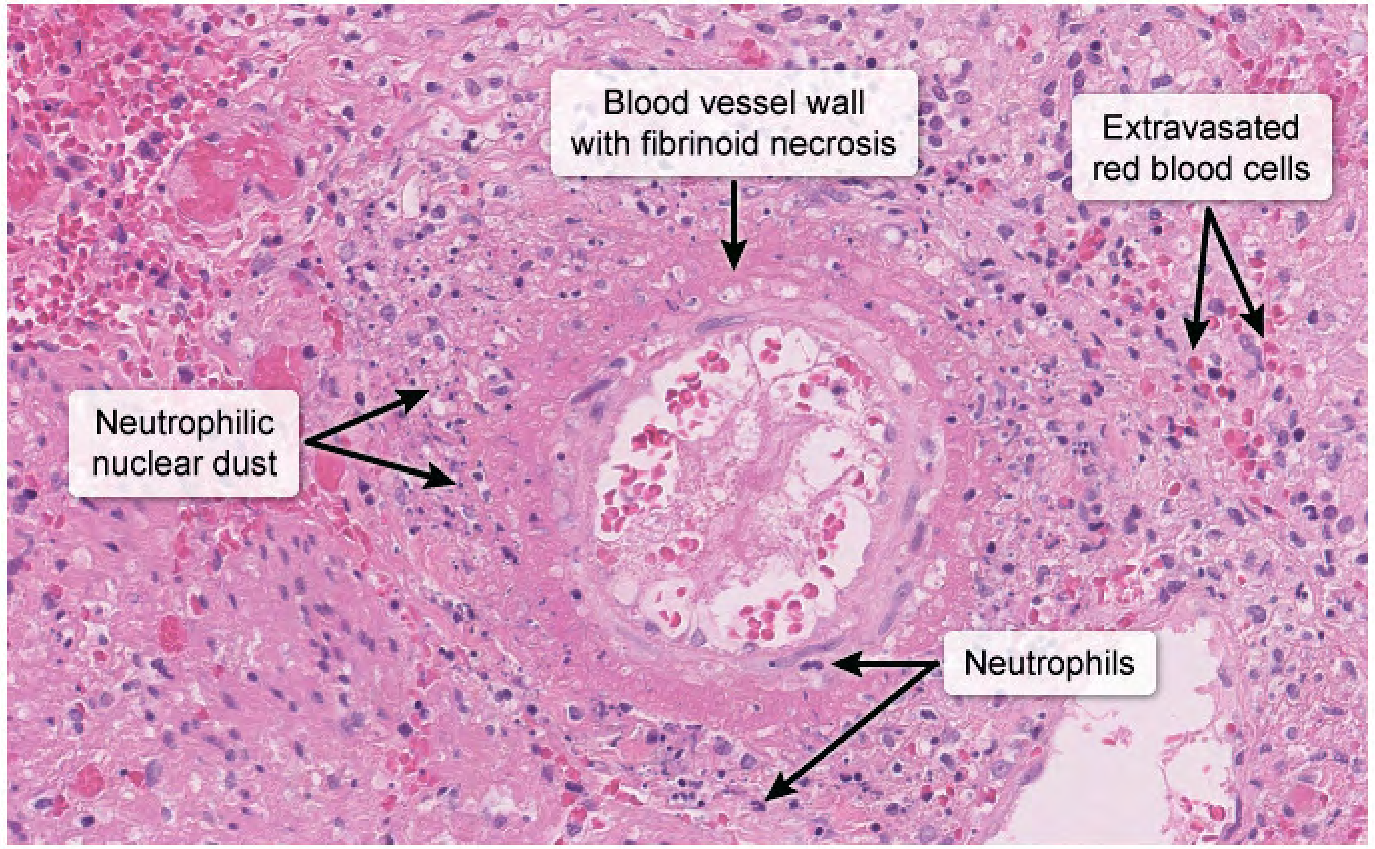
Leukocytoclastic vasculitis


Blood vessel wall with fibrinoid necrosis
Extravasated red blood cells
Neutrophilic nuclear dust
Neutrophils

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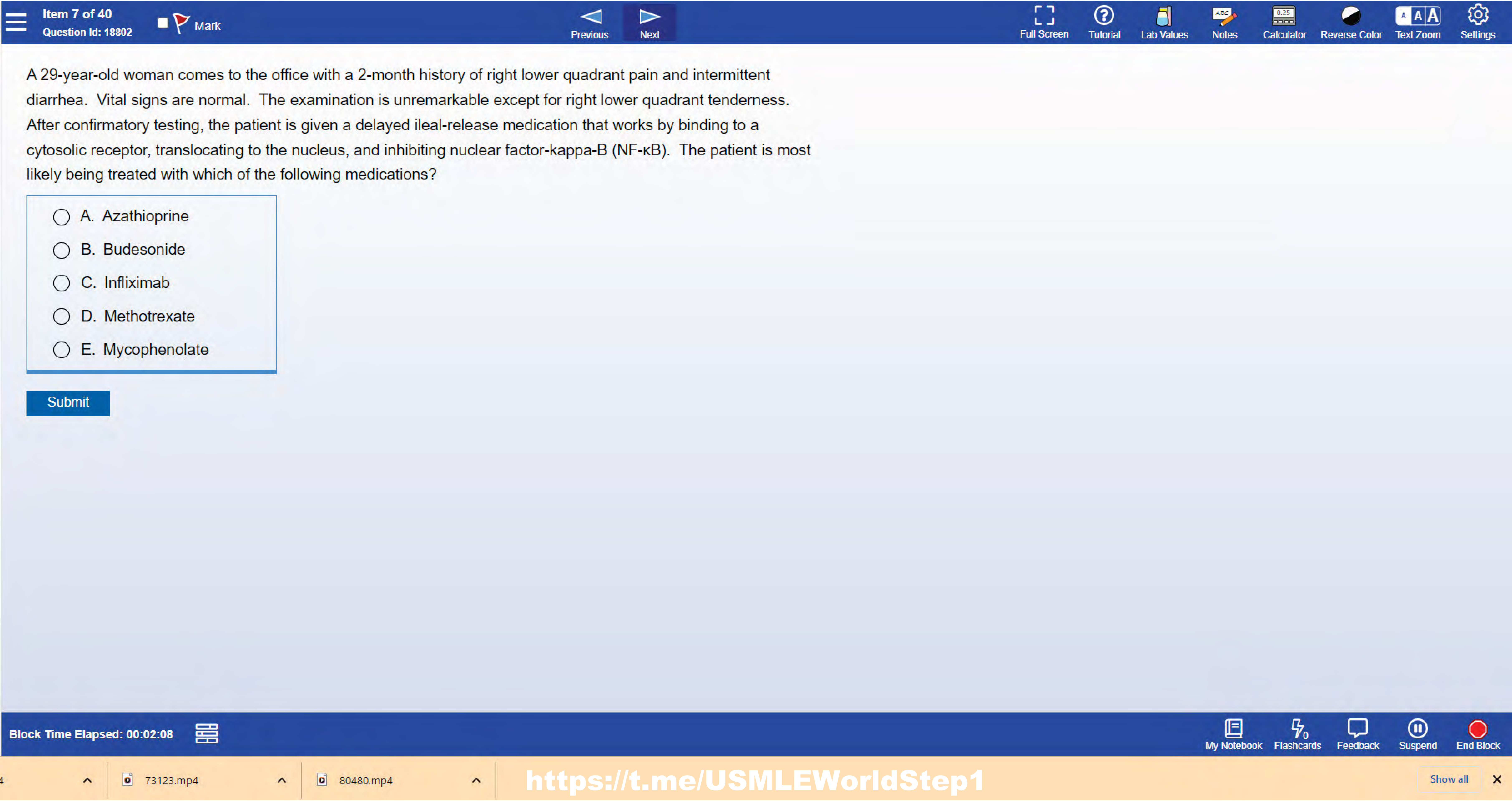
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A 29-year-old woman comes to the office with a 2-month history of right lower quadrant pain and intermittent diarrhea. Vital signs are normal. The examination is unremarkable except for right lower quadrant tenderness. After confirmatory testing, the patient is given a delayed ileal-release medication that works by binding to a cytosolic receptor, translocating to the nucleus, and inhibiting nuclear factor-kappa-B (NF-κB). The patient is most likely being treated with which of the following medications?

- ○ A. Azathioprine
- ○ B. Budesonide
- ○ C. Infliximab
- ○ D. Methotrexate
- ○ E. Mycophenolate

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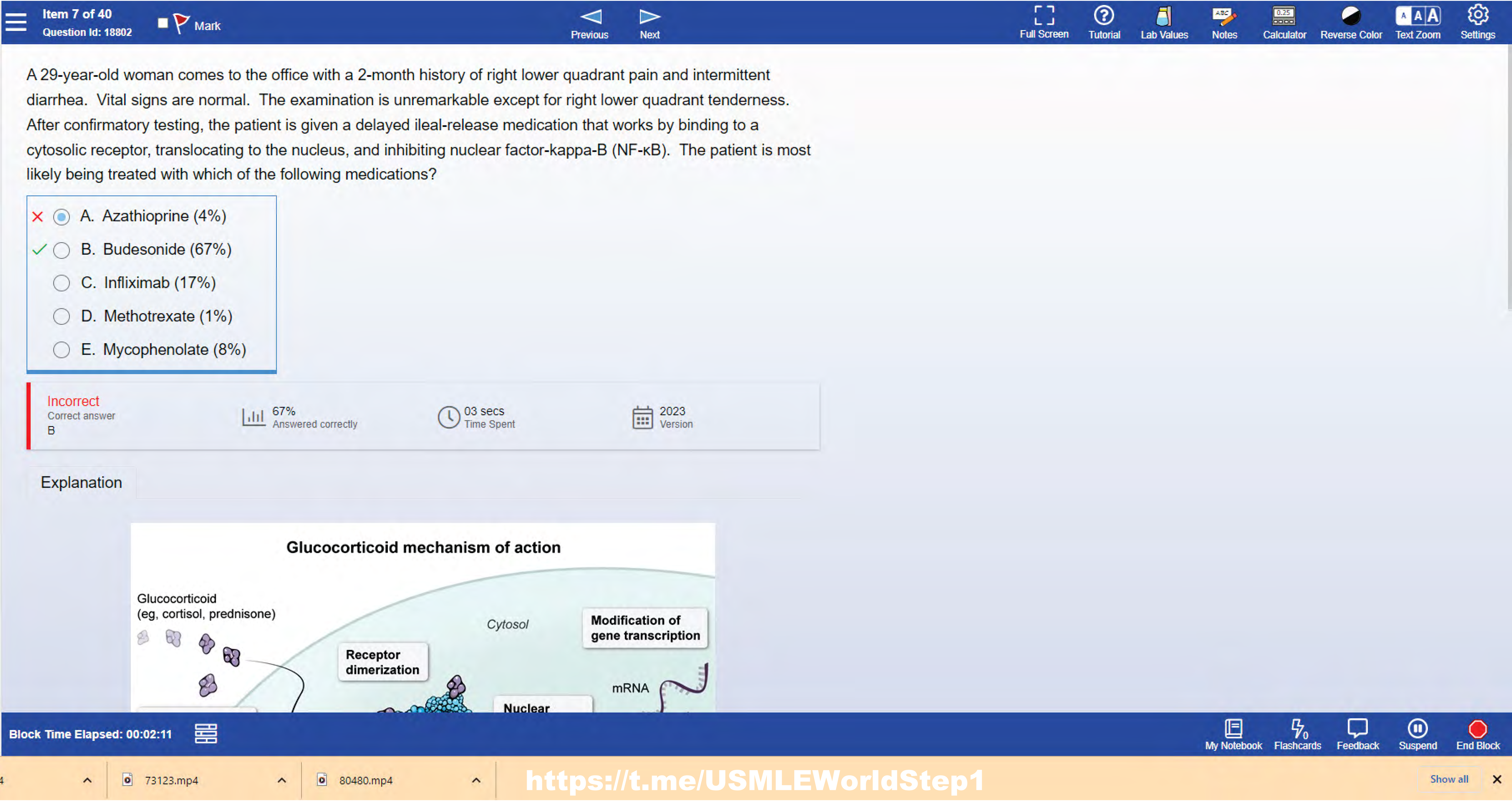
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- ✗ ● A. Azathioprine (4%)
- ✓ ○ B. Budesonide (67%)
- ○ C. Infliximab (17%)
- ○ D. Methotrexate (1%)
- ○ E. Mycophenolate (8%)

Incorrect
Correct answer
B

67%
Answered correctly

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Explanation

Glucocorticoid mechanism of action

Glucocorticoid
(eg, cortisol, prednisone)
Cytosol
Modification of gene transcription
Receptor dimerization
mRNA
Nuclear

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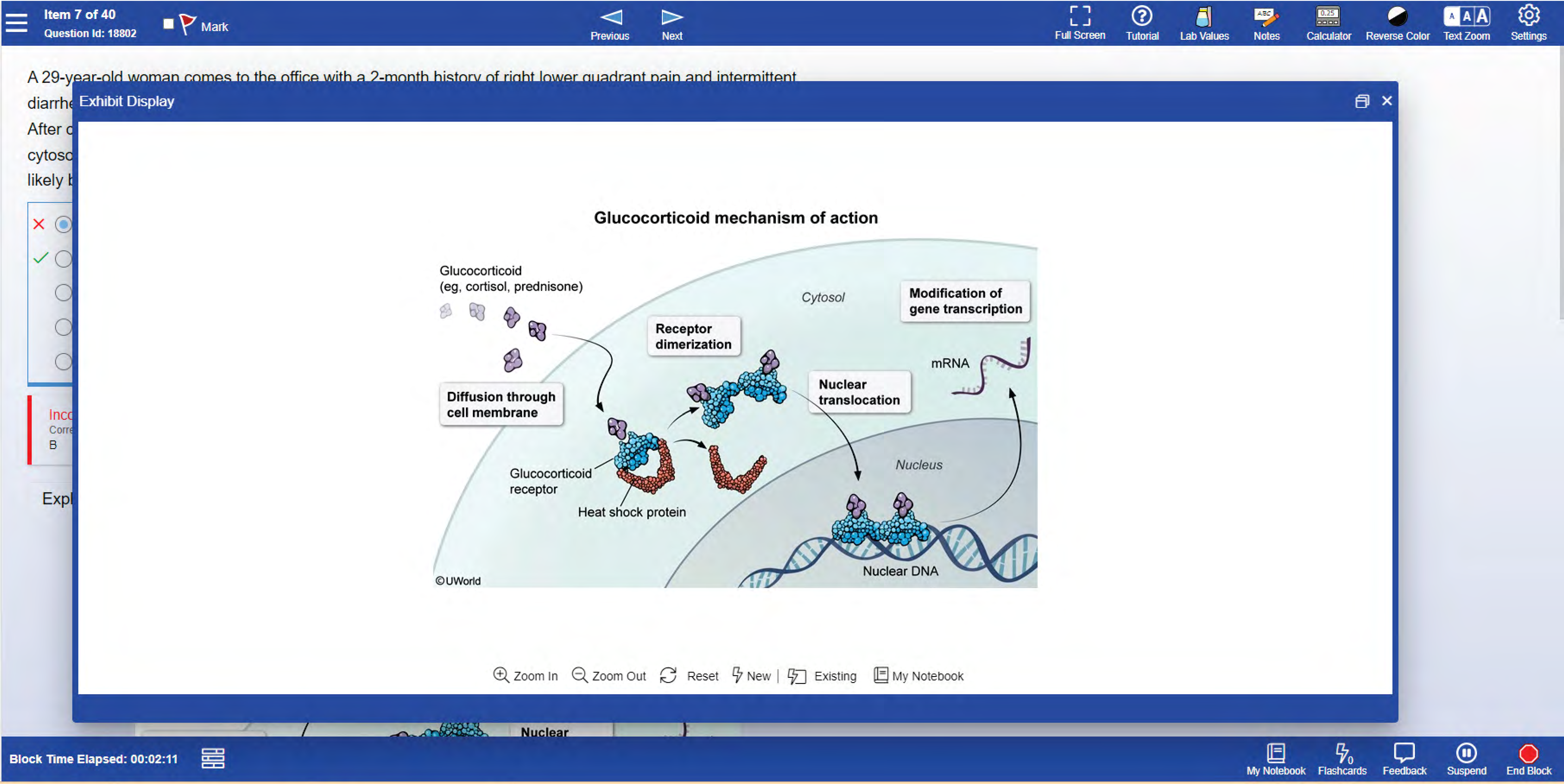
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Glucocorticoid mechanism of action
Glucocorticoid
(eg, cortisol, prednisone)
Diffusion through cell membrane
Glucocorticoid receptor
Heat shock protein
Receptor dimerization
Cytosol
Nuclear translocation
Modification of gene transcription
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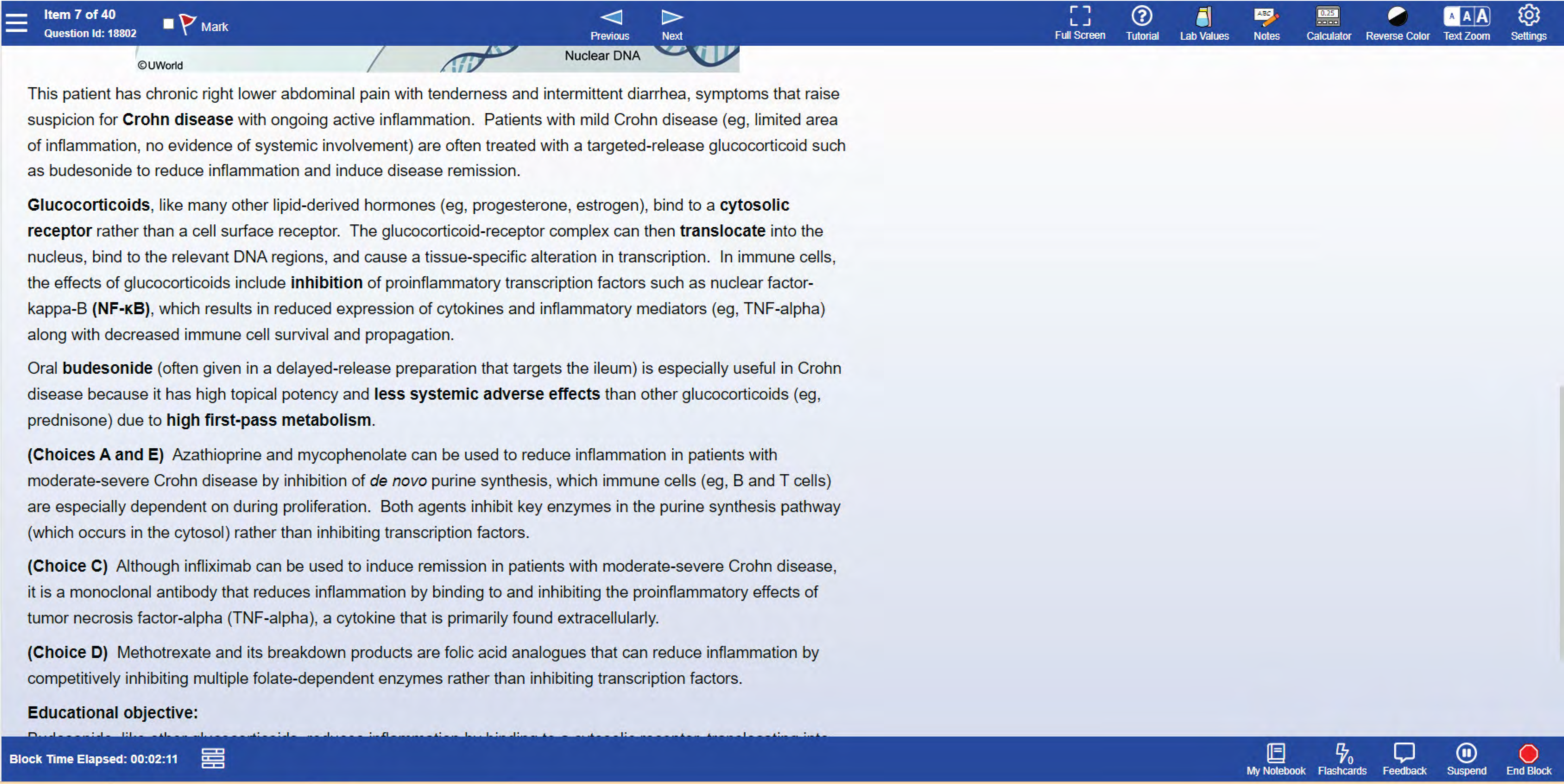

This patient has chronic right lower abdominal pain with tenderness and intermittent diarrhea, symptoms that raise suspicion for **Crohn disease** with ongoing active inflammation. Patients with mild Crohn disease (eg, limited area of inflammation, no evidence of systemic involvement) are often treated with a targeted-release glucocorticoid such as budesonide to reduce inflammation and induce disease remission.

Glucocorticoids, like many other lipid-derived hormones (eg, progesterone, estrogen), bind to a **cytosolic receptor** rather than a cell surface receptor. The glucocorticoid-receptor complex can then **translocate** into the nucleus, bind to the relevant DNA regions, and cause a tissue-specific alteration in transcription. In immune cells, the effects of glucocorticoids include **inhibition** of proinflammatory transcription factors such as nuclear factor-kappa-B **(NF-κB)**, which results in reduced expression of cytokines and inflammatory mediators (eg, TNF-alpha) along with decreased immune cell survival and propagation.

Oral **budesonide** (often given in a delayed-release preparation that targets the ileum) is especially useful in Crohn disease because it has high topical potency and **less systemic adverse effects** than other glucocorticoids (eg, prednisone) due to **high first-pass metabolism**.

(Choices A and E) Azathioprine and mycophenolate can be used to reduce inflammation in patients with moderate-severe Crohn disease by inhibition of *de novo* purine synthesis, which immune cells (eg, B and T cells) are especially dependent on during proliferation. Both agents inhibit key enzymes in the purine synthesis pathway (which occurs in the cytosol) rather than inhibiting transcription factors.

(Choice C) Although infliximab can be used to induce remission in patients with moderate-severe Crohn disease, it is a monoclonal antibody that reduces inflammation by binding to and inhibiting the proinflammatory effects of tumor necrosis factor-alpha (TNF-alpha), a cytokine that is primarily found extracellularly.

(Choice D) Methotrexate and its breakdown products are folic acid analogues that can reduce inflammation by competitively inhibiting multiple folate-dependent enzymes rather than inhibiting transcription factors.

Educational objective:

Budesonide, like other glucocorticoids, reduces inflammation by binding to a cytosolic receptor, translocating into

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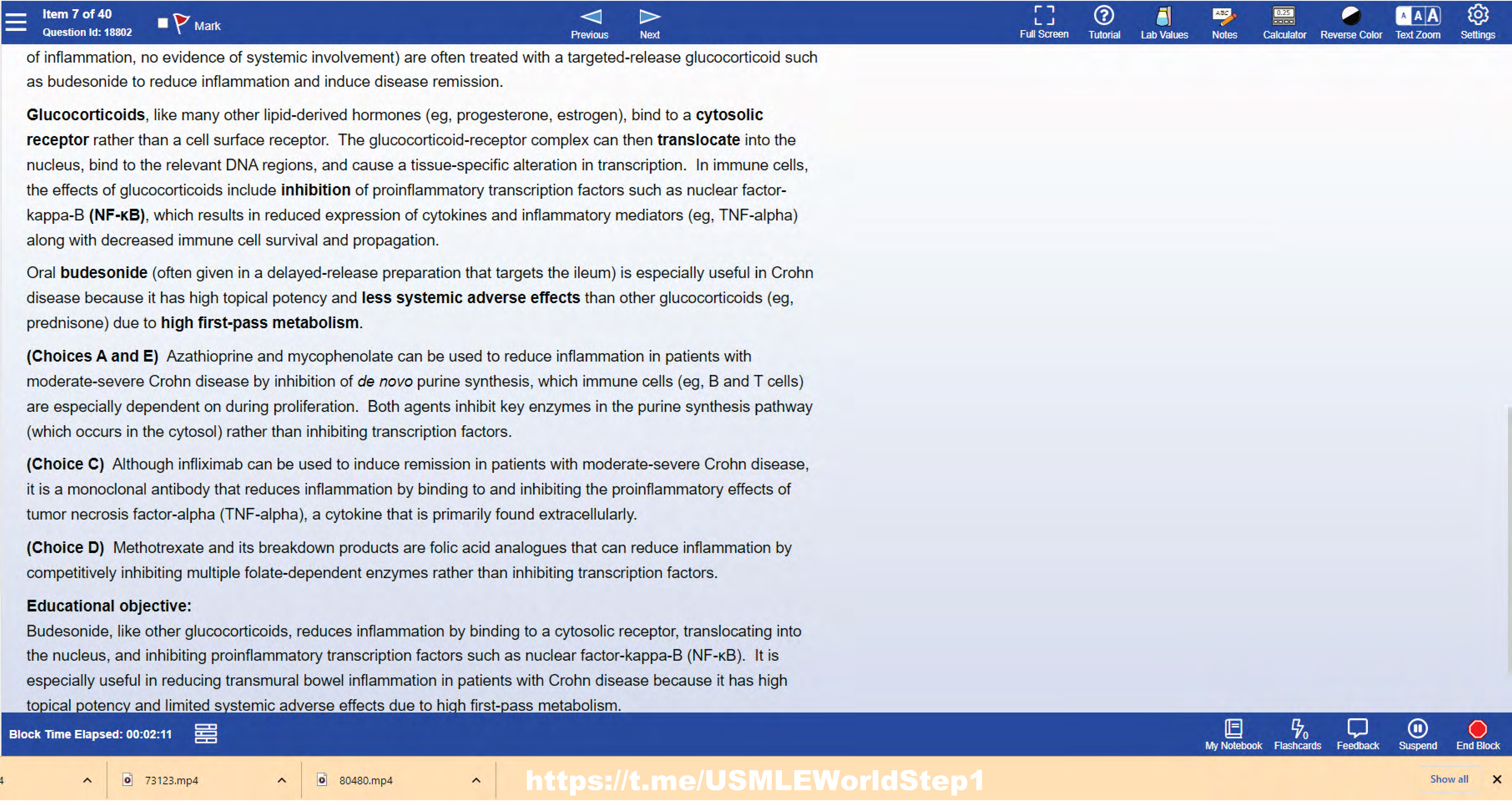

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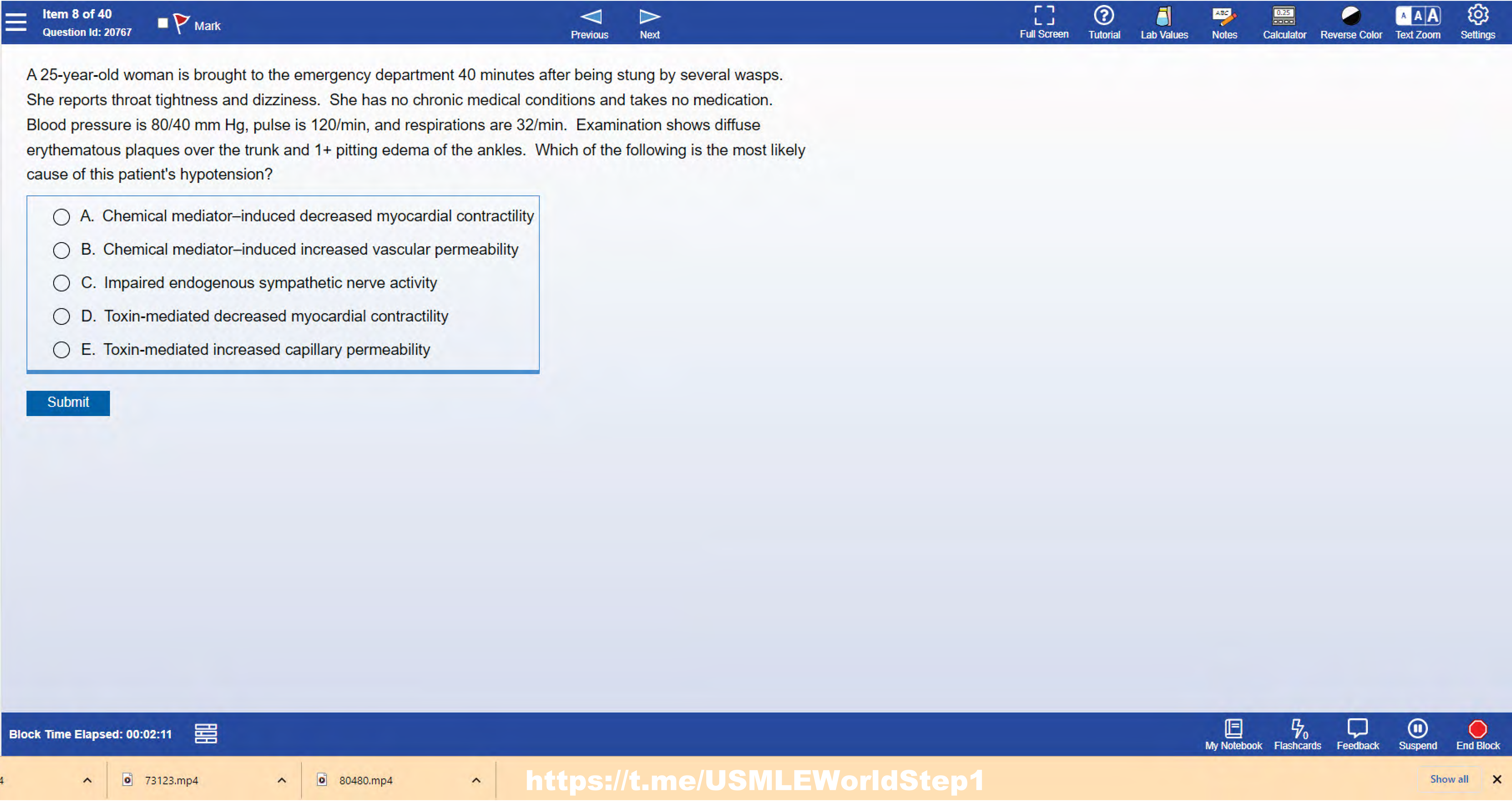
(Choice D) Methotrexate and its breakdown products are folic acid analogues that can reduce inflammation by competitively inhibiting multiple folate-dependent enzymes rather than inhibiting transcription factors.

Educational objective:

Budesonide, like other glucocorticoids, reduces inflammation by binding to a cytosolic receptor, translocating into the nucleus, and inhibiting proinflammatory transcription factors such as nuclear factor-kappa-B (NF-κB). It is especially useful in reducing transmural bowel inflammation in patients with Crohn disease because it has high topical potency and limited systemic adverse effects due to high first-pass metabolism.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A 25-year-old woman is brought to the emergency department 40 minutes after being stung by several wasps. She reports throat tightness and dizziness. She has no chronic medical conditions and takes no medication. Blood pressure is 80/40 mm Hg, pulse is 120/min, and respirations are 32/min. Examination shows diffuse erythematous plaques over the trunk and 1+ pitting edema of the ankles. Which of the following is the most likely cause of this patient's hypotension?

- ○ A. Chemical mediator–induced decreased myocardial contractility
- ○ B. Chemical mediator–induced increased vascular permeability
- ○ C. Impaired endogenous sympathetic nerve activity
- ○ D. Toxin-mediated decreased myocardial contractility
- ○ E. Toxin-mediated increased capillary permeability

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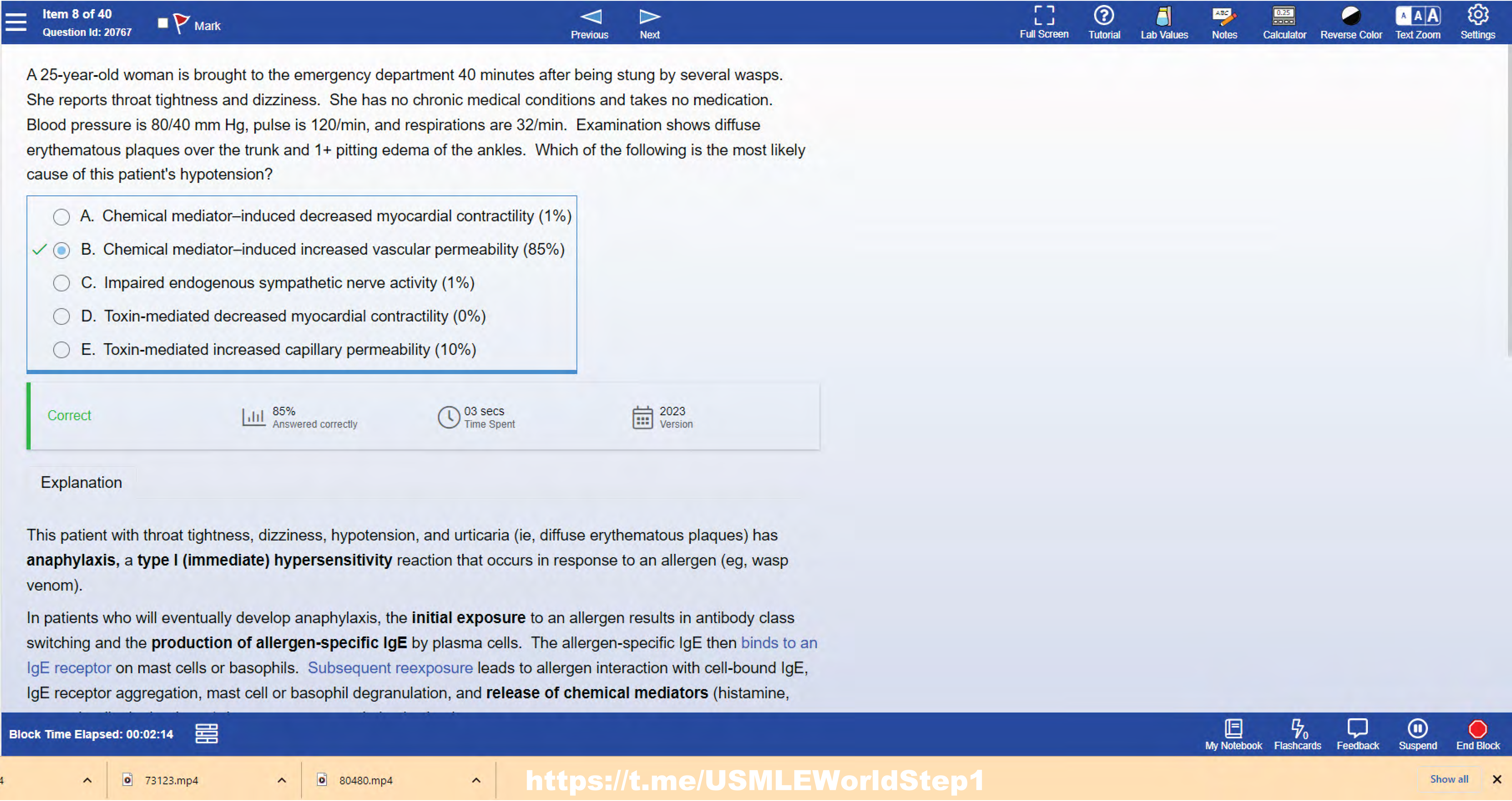
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○ A. Chemical mediator–induced decreased myocardial contractility (1%)

✓ ● B. Chemical mediator–induced increased vascular permeability (85%)

○ C. Impaired endogenous sympathetic nerve activity (1%)

○ D. Toxin-mediated decreased myocardial contractility (0%)

○ E. Toxin-mediated increased capillary permeability (10%)

Correct

85% Answered correctly

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2023 Version

Explanation

This patient with throat tightness, dizziness, hypotension, and urticaria (ie, diffuse erythematous plaques) has **anaphylaxis,** a **type I (immediate) hypersensitivity** reaction that occurs in response to an allergen (eg, wasp venom).

In patients who will eventually develop anaphylaxis, the **initial exposure** to an allergen results in antibody class switching and the **production of allergen-specific IgE** by plasma cells. The allergen-specific IgE then binds to an IgE receptor on mast cells or basophils. Subsequent reexposure leads to allergen interaction with cell-bound IgE, IgE receptor aggregation, mast cell or basophil degranulation, and **release of chemical mediators** (histamine,

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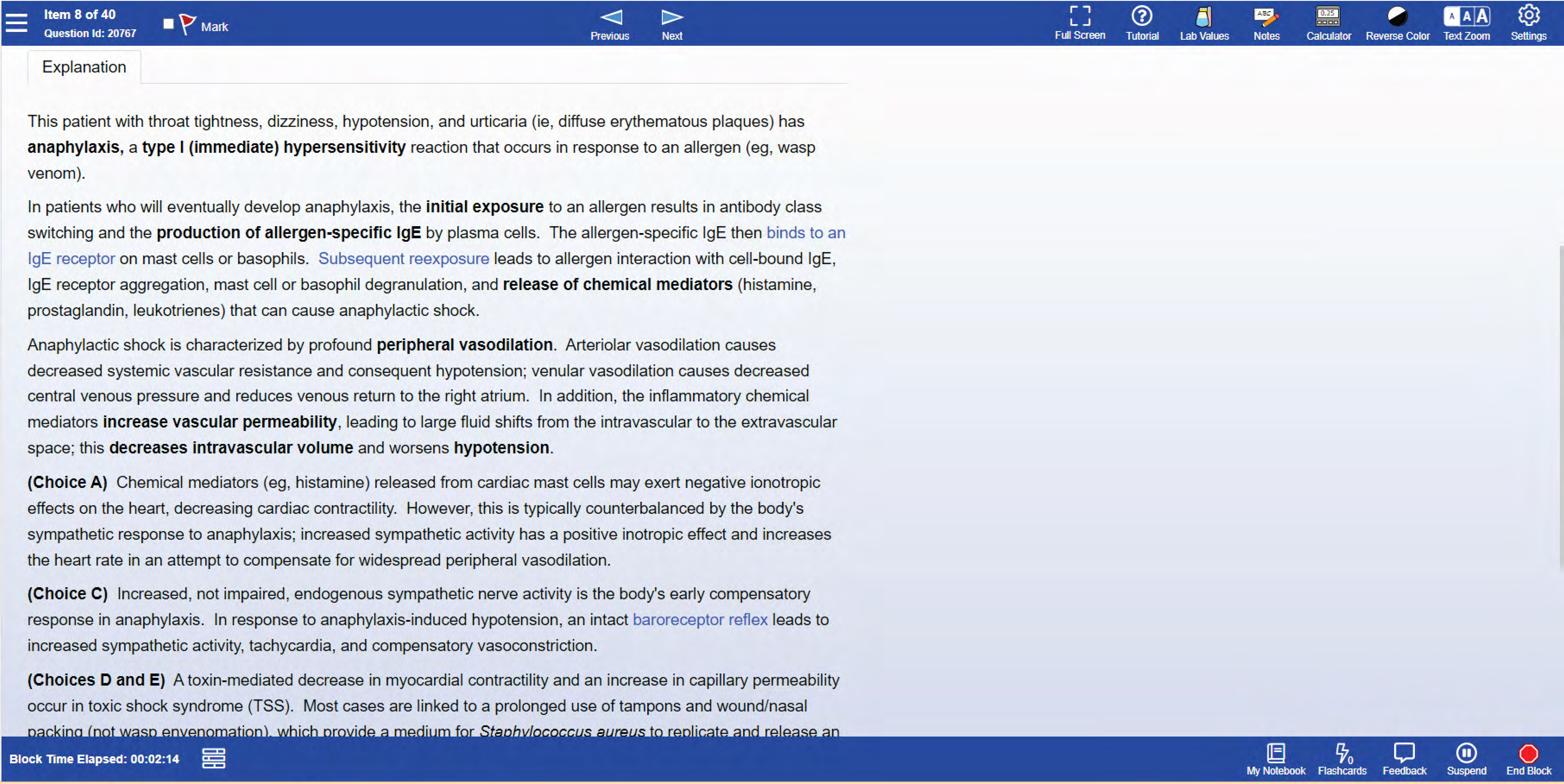

This patient with throat tightness, dizziness, hypotension, and urticaria (ie, diffuse erythematous plaques) has **anaphylaxis,** a **type I (immediate) hypersensitivity** reaction that occurs in response to an allergen (eg, wasp venom).

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Anaphylactic shock is characterized by profound **peripheral vasodilation**. Arteriolar vasodilation causes decreased systemic vascular resistance and consequent hypotension; venular vasodilation causes decreased central venous pressure and reduces venous return to the right atrium. In addition, the inflammatory chemical mediators **increase vascular permeability**, leading to large fluid shifts from the intravascular to the extravascular space; this **decreases intravascular volume** and worsens **hypotension**.

(Choice A) Chemical mediators (eg, histamine) released from cardiac mast cells may exert negative ionotropic effects on the heart, decreasing cardiac contractility. However, this is typically counterbalanced by the body's sympathetic response to anaphylaxis; increased sympathetic activity has a positive inotropic effect and increases the heart rate in an attempt to compensate for widespread peripheral vasodilation.

(Choice C) Increased, not impaired, endogenous sympathetic nerve activity is the body's early compensatory response in anaphylaxis. In response to anaphylaxis-induced hypotension, an intact baroreceptor reflex leads to increased sympathetic activity, tachycardia, and compensatory vasoconstriction.

(Choices D and E) A toxin-mediated decrease in myocardial contractility and an increase in capillary permeability occur in toxic shock syndrome (TSS). Most cases are linked to a prolonged use of tampons and wound/nasal packing (not wasp envenomation), which provide a medium for *Staphylococcus aureus* to replicate and release an

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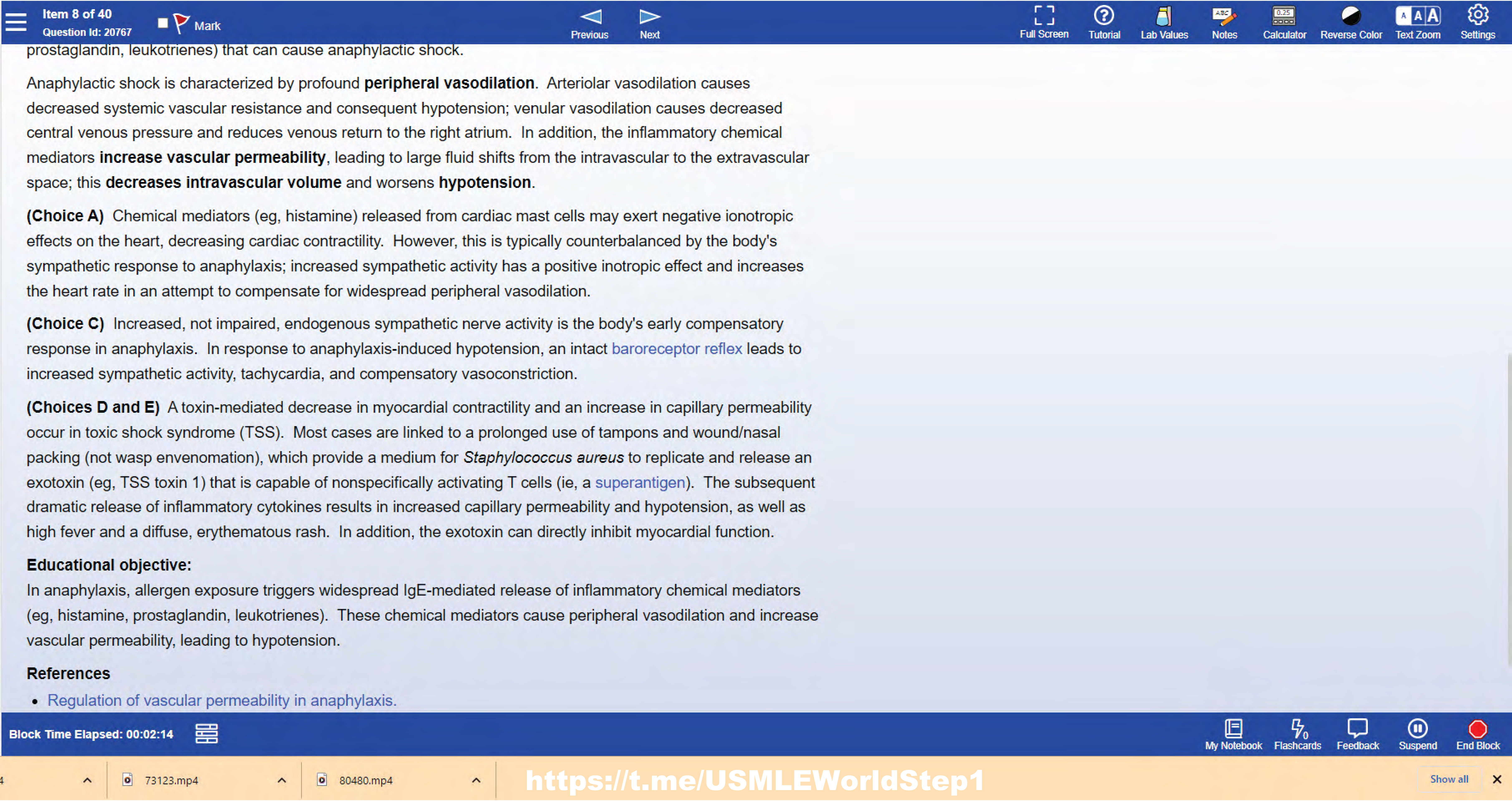

prostaglandin, leukotrienes) that can cause anaphylactic shock.

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(Choices D and E) A toxin-mediated decrease in myocardial contractility and an increase in capillary permeability occur in toxic shock syndrome (TSS). Most cases are linked to a prolonged use of tampons and wound/nasal packing (not wasp envenomation), which provide a medium for *Staphylococcus aureus* to replicate and release an exotoxin (eg, TSS toxin 1) that is capable of nonspecifically activating T cells (ie, a superantigen). The subsequent dramatic release of inflammatory cytokines results in increased capillary permeability and hypotension, as well as high fever and a diffuse, erythematous rash. In addition, the exotoxin can directly inhibit myocardial function.

Educational objective:

In anaphylaxis, allergen exposure triggers widespread IgE-mediated release of inflammatory chemical mediators (eg, histamine, prostaglandin, leukotrienes). These chemical mediators cause peripheral vasodilation and increase vascular permeability, leading to hypotension.

References

- Regulation of vascular permeability in anaphylaxis.

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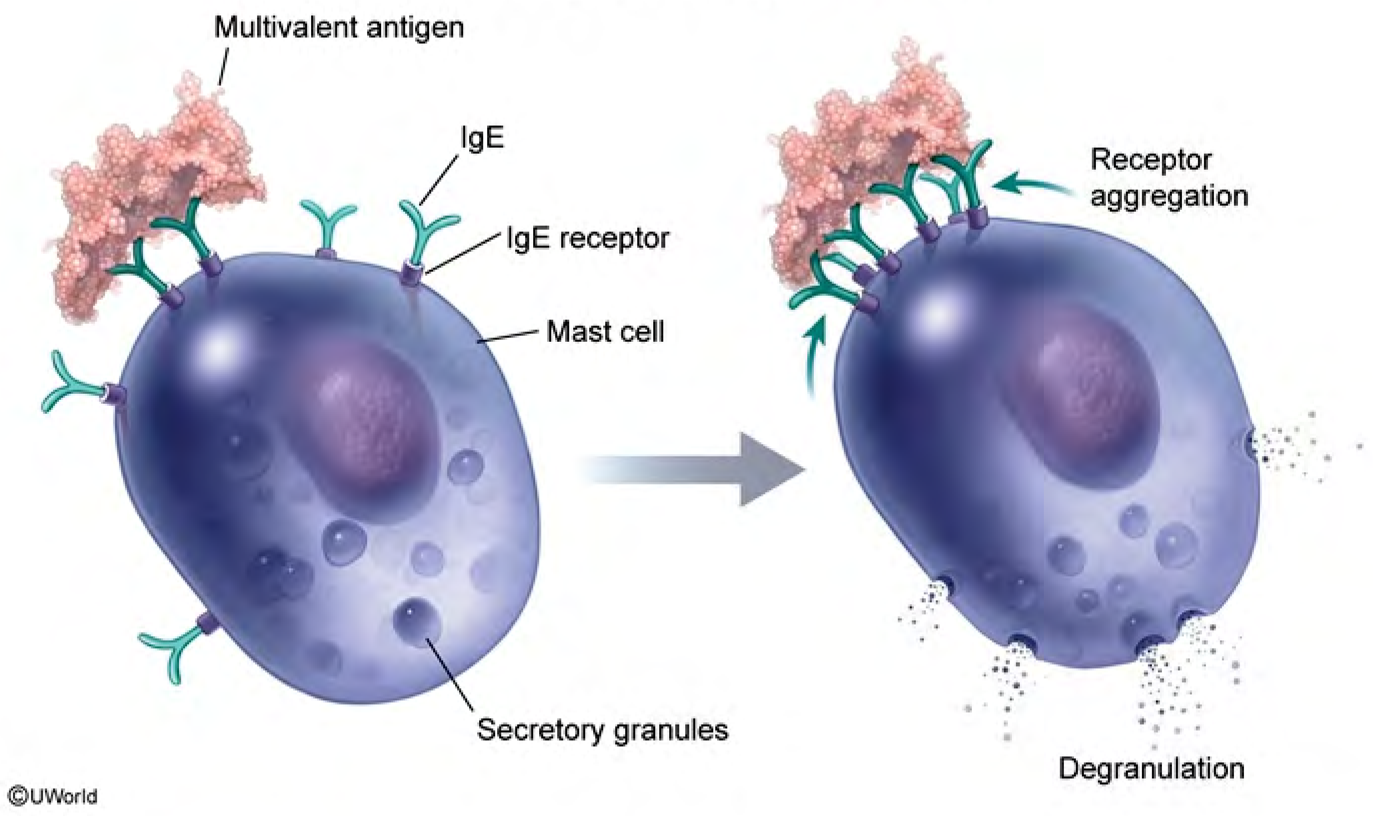
High-affinity IgE receptor activation


Multivalent antigen
IgE
IgE receptor
Mast cell
Secretory granules
Receptor aggregation
Degranulation
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occur in toxic shock syndrome (TSS). Most cases are linked to a prolonged use of tampons and wound/nasal packing (not wasp envenomation), which provide a medium for *Staphylococcus aureus* to replicate and release an

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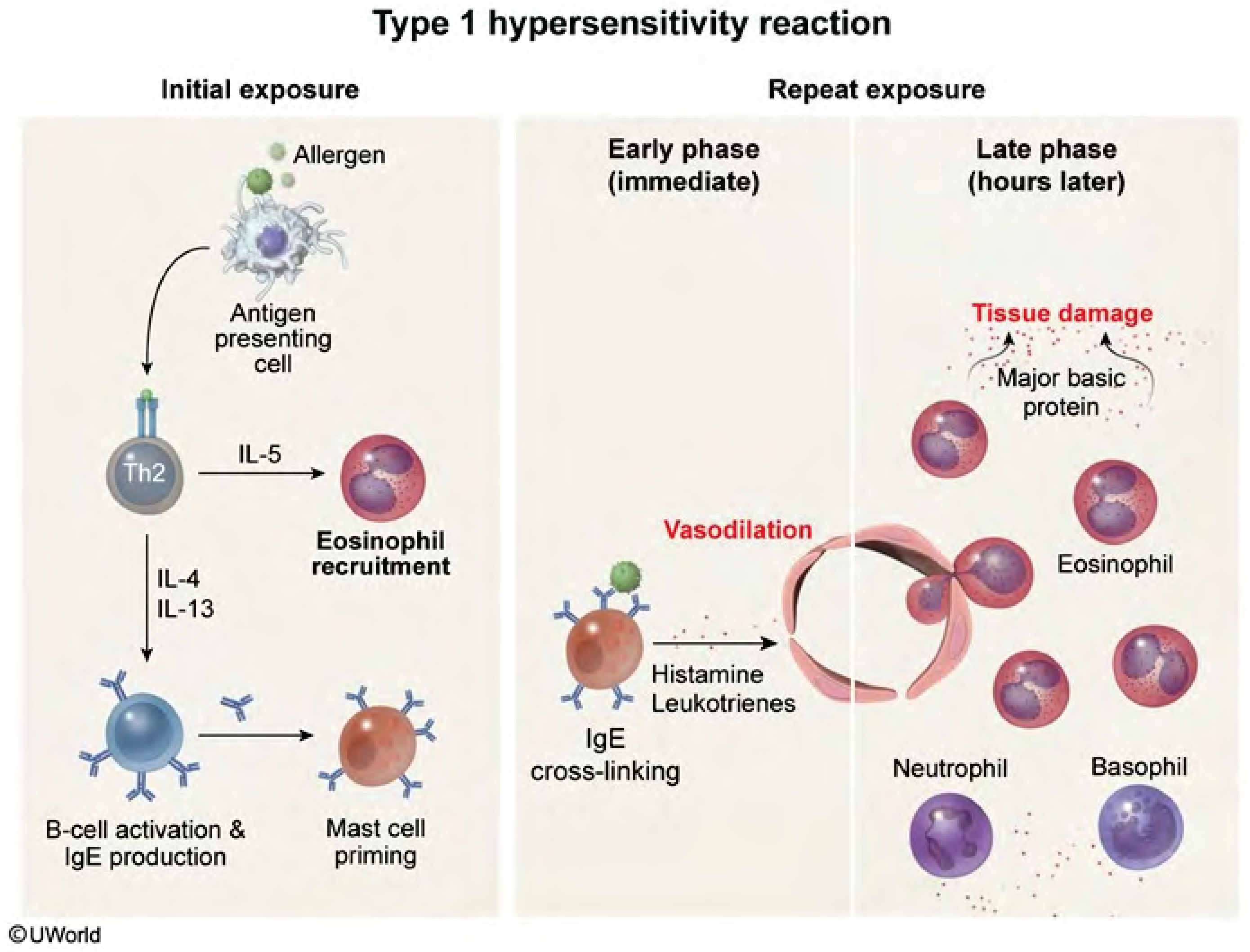

Type 1 hypersensitivity reaction

Initial exposure
Repeat exposure
Early phase (immediate)
Late phase (hours later)
Allergen
Antigen presenting cell
Th2
IL-5
Eosinophil recruitment
IL-4
IL-13
B-cell activation & IgE production
Mast cell priming
Vasodilation
Histamine
Leukotrienes
IgE cross-linking
Tissue damage
Major basic protein
Eosinophil
Neutrophil
Basophil

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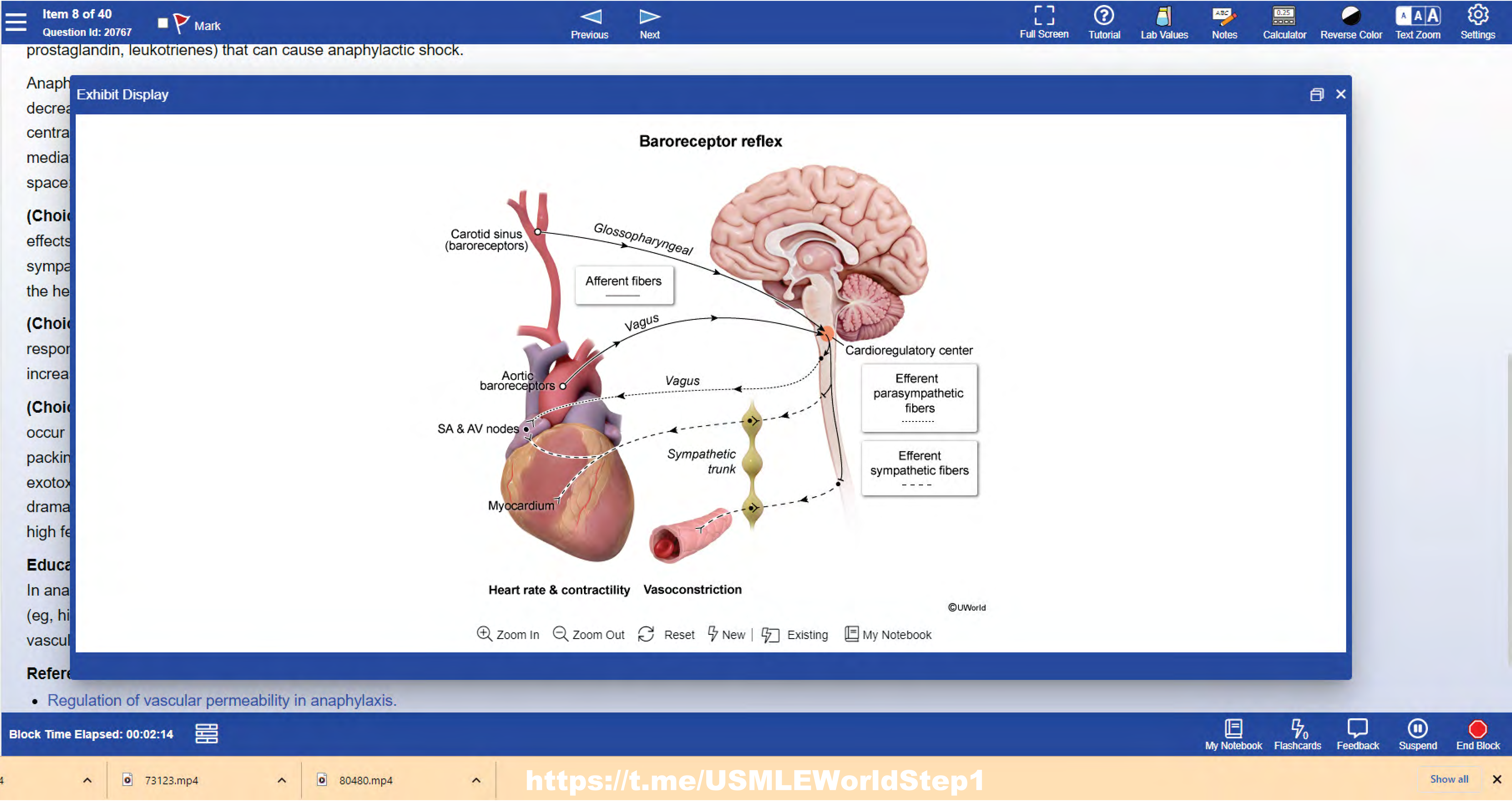
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- Regulation of vascular permeability in anaphylaxis.

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Baroreceptor reflex

Carotid sinus
(baroreceptors)
Glossopharyngeal
Afferent fibers
Vagus
Aortic
baroreceptors
Cardioregulatory center
Vagus
Efferent
parasympathetic
fibers
SA & AV nodes
Sympathetic
trunk
Efferent
sympathetic fibers
Myocardium
Heart rate & contractility
Vasoconstriction

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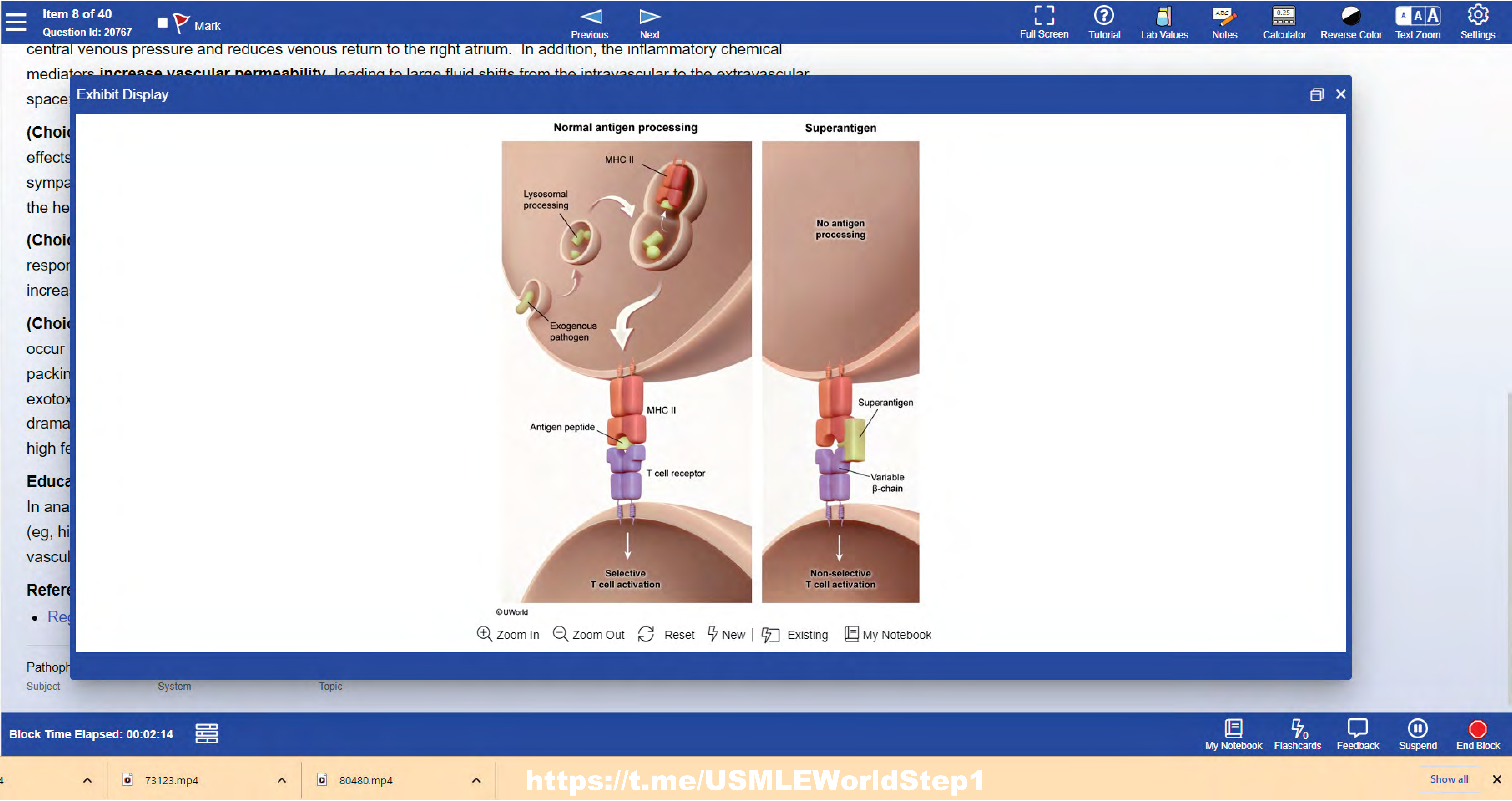

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Normal antigen processing
MHC II
Lysosomal processing
Exogenous pathogen
MHC II
Antigen peptide
T cell receptor
Selective T cell activation
Superantigen
No antigen processing
Superantigen
Variable β-chain
Non-selective T cell activation
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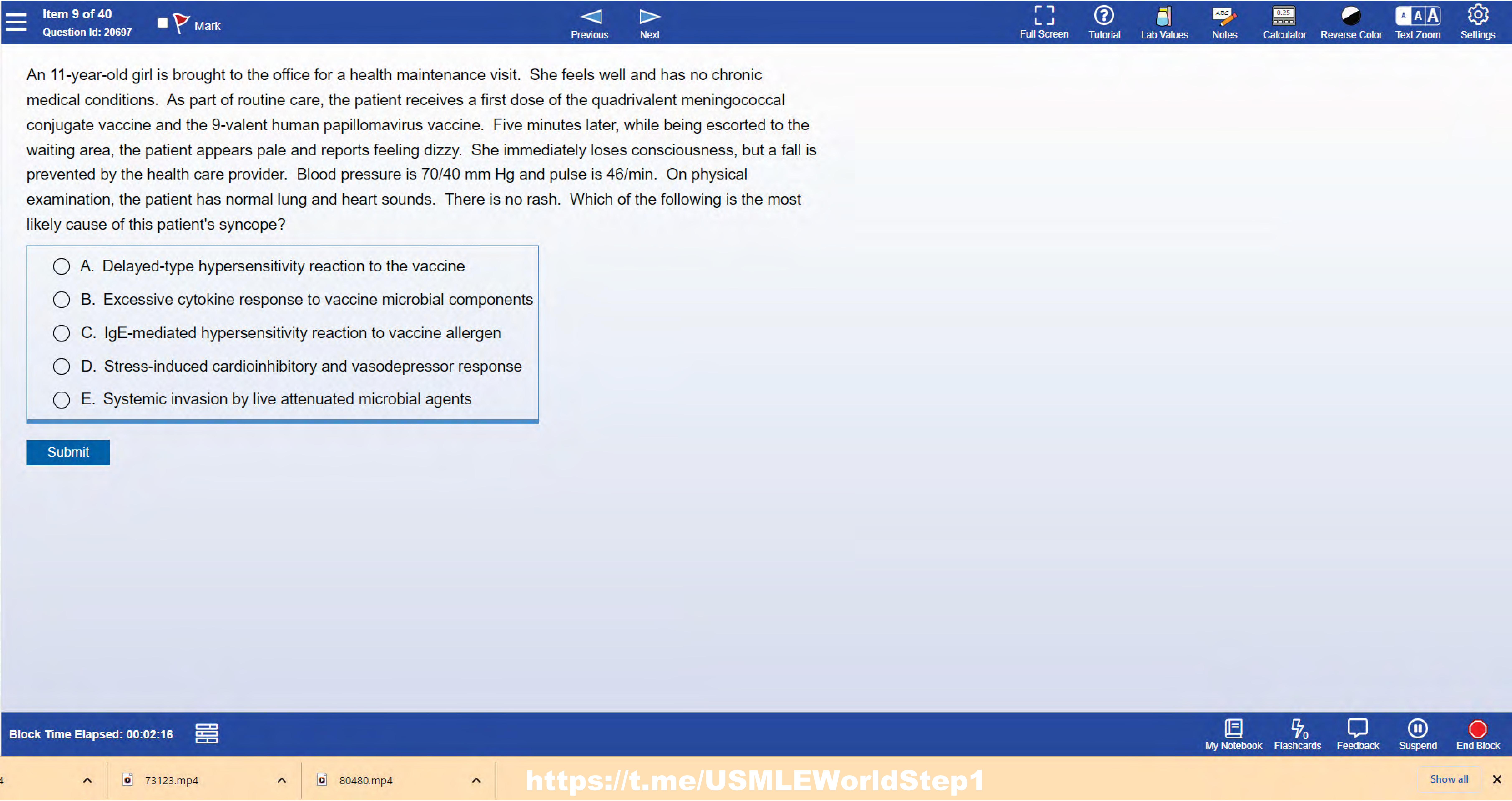
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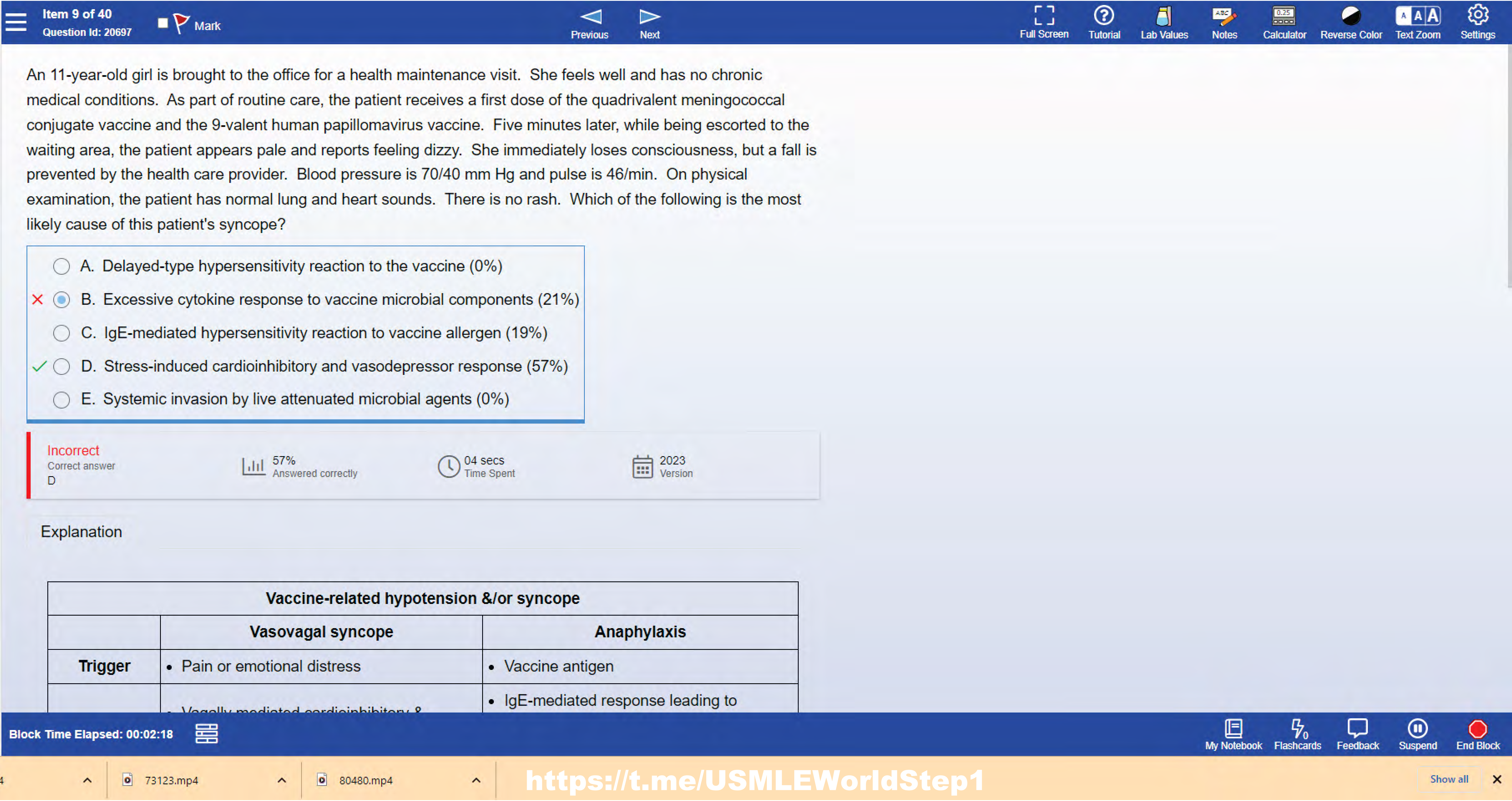
An 11-year-old girl is brought to the office for a health maintenance visit. She feels well and has no chronic medical conditions. As part of routine care, the patient receives a first dose of the quadrivalent meningococcal conjugate vaccine and the 9-valent human papillomavirus vaccine. Five minutes later, while being escorted to the waiting area, the patient appears pale and reports feeling dizzy. She immediately loses consciousness, but a fall is prevented by the health care provider. Blood pressure is 70/40 mm Hg and pulse is 46/min. On physical examination, the patient has normal lung and heart sounds. There is no rash. Which of the following is the most likely cause of this patient's syncope?

○ A. Delayed-type hypersensitivity reaction to the vaccine
○ B. Excessive cytokine response to vaccine microbial components
○ C. IgE-mediated hypersensitivity reaction to vaccine allergen
○ D. Stress-induced cardioinhibitory and vasodepressor response
○ E. Systemic invasion by live attenuated microbial agents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An 11-year-old girl is brought to the office for a health maintenance visit. She feels well and has no chronic medical conditions. As part of routine care, the patient receives a first dose of the quadrivalent meningococcal conjugate vaccine and the 9-valent human papillomavirus vaccine. Five minutes later, while being escorted to the waiting area, the patient appears pale and reports feeling dizzy. She immediately loses consciousness, but a fall is prevented by the health care provider. Blood pressure is 70/40 mm Hg and pulse is 46/min. On physical examination, the patient has normal lung and heart sounds. There is no rash. Which of the following is the most likely cause of this patient's syncope?

- ○ A. Delayed-type hypersensitivity reaction to the vaccine (0%)
- ✗ ● B. Excessive cytokine response to vaccine microbial components (21%)
- ○ C. IgE-mediated hypersensitivity reaction to vaccine allergen (19%)
- ✓ ○ D. Stress-induced cardioinhibitory and vasodepressor response (57%)
- ○ E. Systemic invasion by live attenuated microbial agents (0%)

Incorrect
Correct answer
D

57%
Answered correctly

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Explanation

Vaccine-related hypotension &/or syncope		
	Vasovagal syncope	**Anaphylaxis**
Trigger	• Pain or emotional distress	• Vaccine antigen
	• Vagally mediated cardioinhibitory &	• IgE-mediated response leading to

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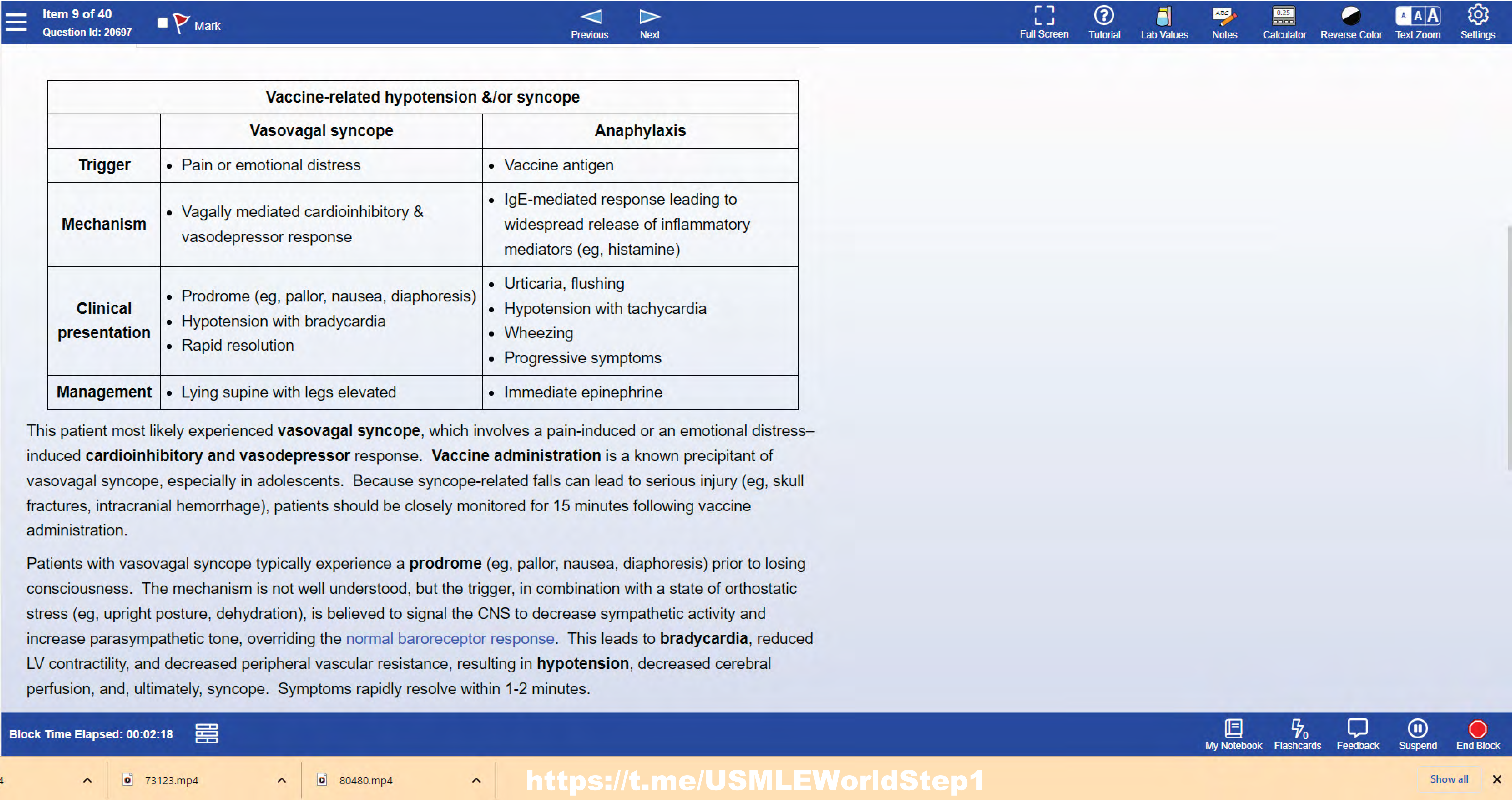
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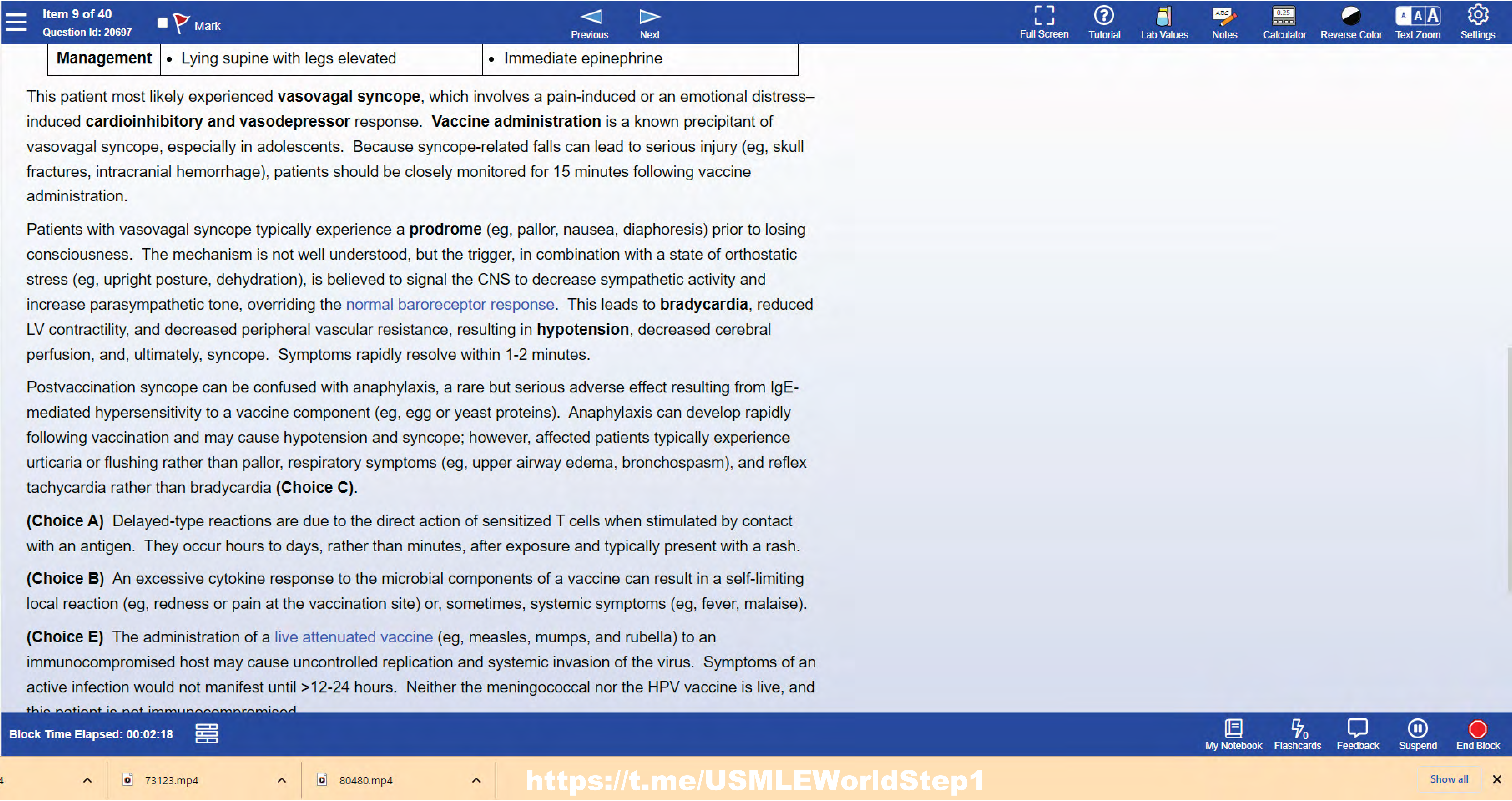
Vaccine-related hypotension &/or syncope		
	Vasovagal syncope	**Anaphylaxis**
Trigger	• Pain or emotional distress	• Vaccine antigen
Mechanism	• Vagally mediated cardioinhibitory & vasodepressor response	• IgE-mediated response leading to widespread release of inflammatory mediators (eg, histamine)
Clinical presentation	• Prodrome (eg, pallor, nausea, diaphoresis) • Hypotension with bradycardia • Rapid resolution	• Urticaria, flushing • Hypotension with tachycardia • Wheezing • Progressive symptoms
Management	• Lying supine with legs elevated	• Immediate epinephrine

This patient most likely experienced **vasovagal syncope**, which involves a pain-induced or an emotional distress–induced **cardioinhibitory and vasodepressor** response. **Vaccine administration** is a known precipitant of vasovagal syncope, especially in adolescents. Because syncope-related falls can lead to serious injury (eg, skull fractures, intracranial hemorrhage), patients should be closely monitored for 15 minutes following vaccine administration.

Patients with vasovagal syncope typically experience a **prodrome** (eg, pallor, nausea, diaphoresis) prior to losing consciousness. The mechanism is not well understood, but the trigger, in combination with a state of orthostatic stress (eg, upright posture, dehydration), is believed to signal the CNS to decrease sympathetic activity and increase parasympathetic tone, overriding the normal baroreceptor response. This leads to **bradycardia**, reduced LV contractility, and decreased peripheral vascular resistance, resulting in **hypotension**, decreased cerebral perfusion, and, ultimately, syncope. Symptoms rapidly resolve within 1-2 minutes.



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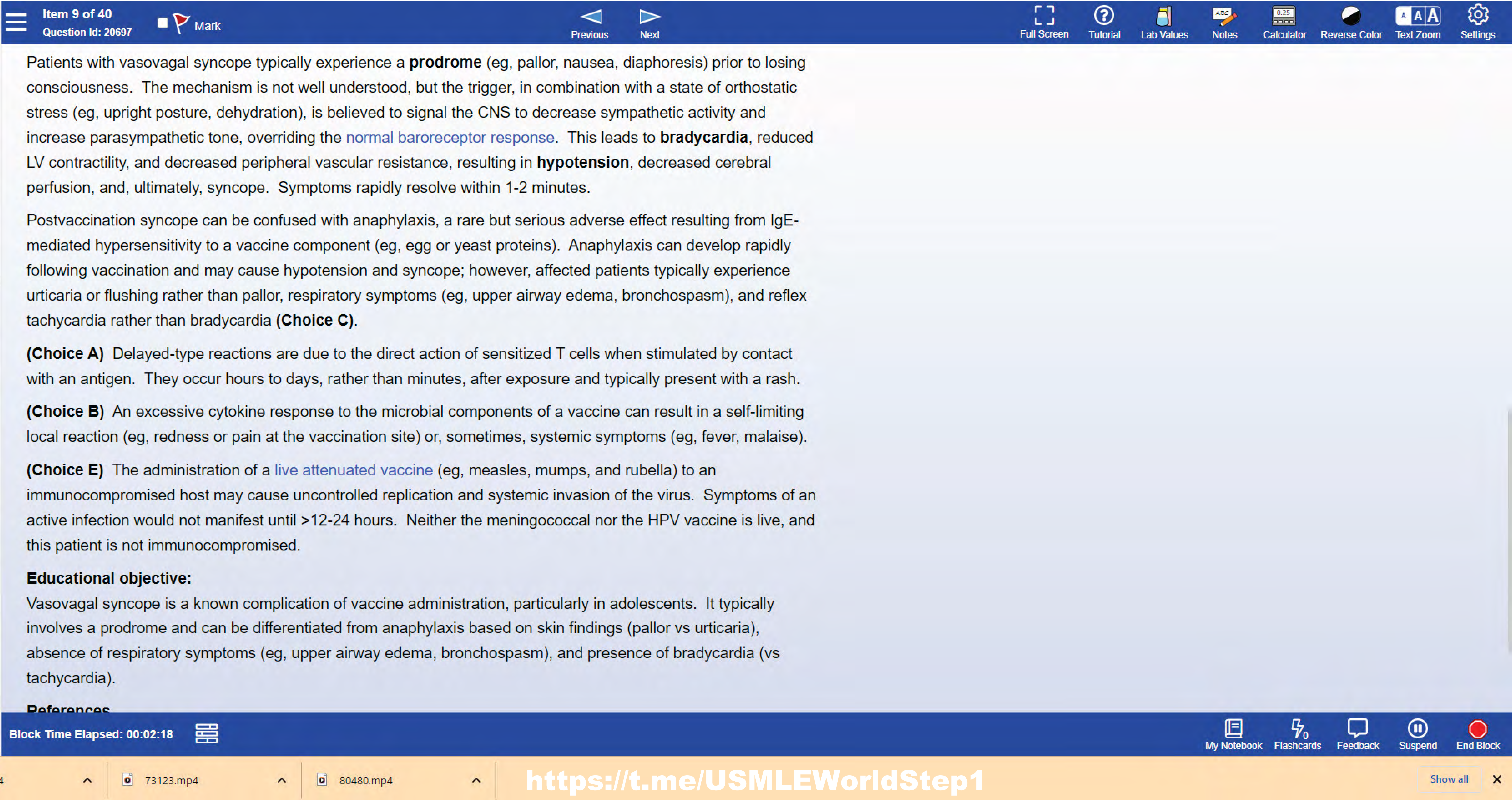
Postvaccination syncope can be confused with anaphylaxis, a rare but serious adverse effect resulting from IgE-mediated hypersensitivity to a vaccine component (eg, egg or yeast proteins). Anaphylaxis can develop rapidly following vaccination and may cause hypotension and syncope; however, affected patients typically experience urticaria or flushing rather than pallor, respiratory symptoms (eg, upper airway edema, bronchospasm), and reflex tachycardia rather than bradycardia **(Choice C)**.

(Choice A) Delayed-type reactions are due to the direct action of sensitized T cells when stimulated by contact with an antigen. They occur hours to days, rather than minutes, after exposure and typically present with a rash.

(Choice B) An excessive cytokine response to the microbial components of a vaccine can result in a self-limiting local reaction (eg, redness or pain at the vaccination site) or, sometimes, systemic symptoms (eg, fever, malaise).

(Choice E) The administration of a live attenuated vaccine (eg, measles, mumps, and rubella) to an immunocompromised host may cause uncontrolled replication and systemic invasion of the virus. Symptoms of an active infection would not manifest until >12-24 hours. Neither the meningococcal nor the HPV vaccine is live, and this patient is not immunocompromised.



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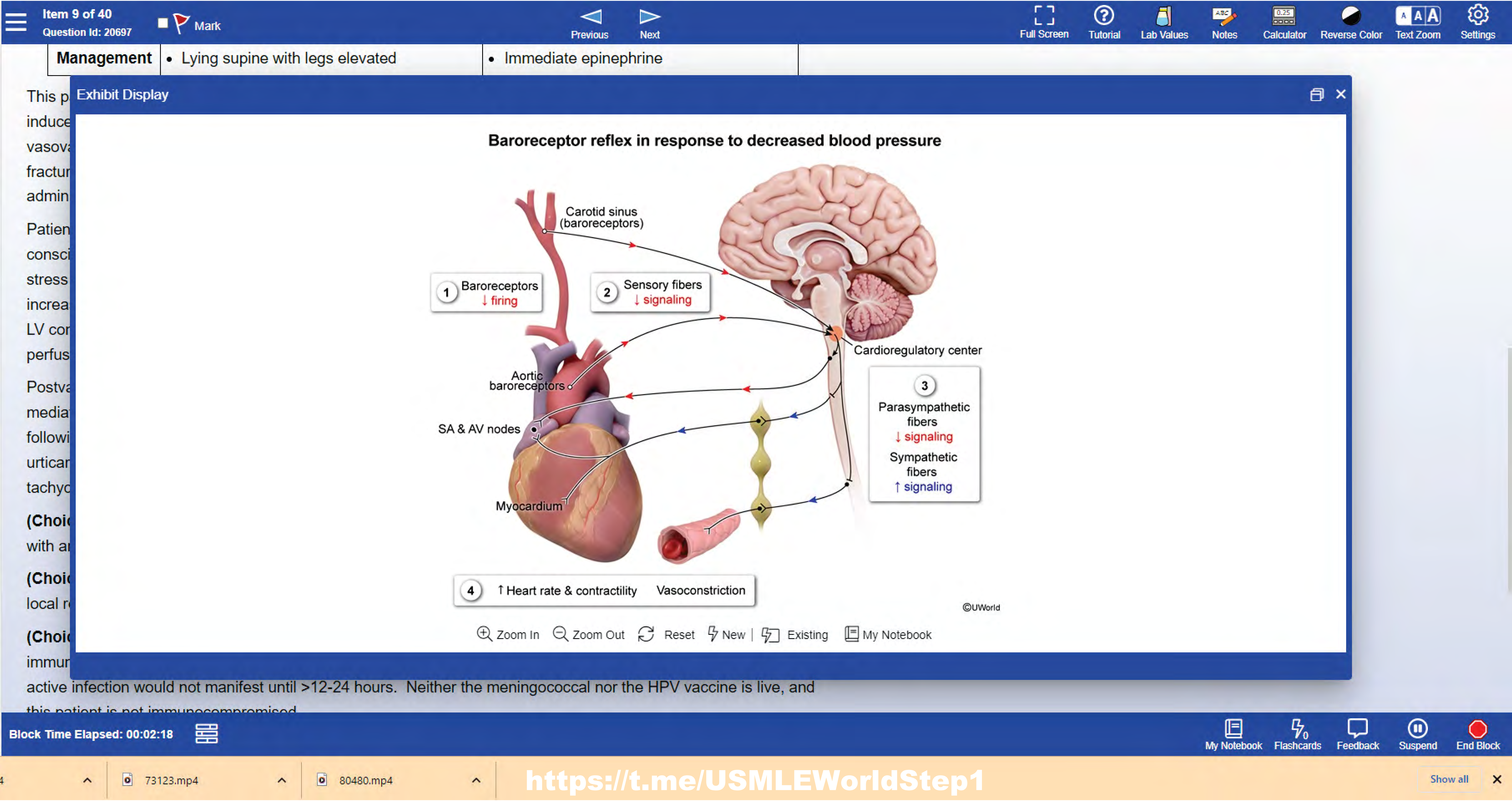
Educational objective:

Vasovagal syncope is a known complication of vaccine administration, particularly in adolescents. It typically involves a prodrome and can be differentiated from anaphylaxis based on skin findings (pallor vs urticaria), absence of respiratory symptoms (eg, upper airway edema, bronchospasm), and presence of bradycardia (vs tachycardia).

References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this patient is not immunocompromised.

Baroreceptor reflex in response to decreased blood pressure

Carotid sinus (baroreceptors)
① Baroreceptors ↓ firing
② Sensory fibers ↓ signaling
Cardioregulatory center
Aortic baroreceptors
SA & AV nodes
③ Parasympathetic fibers ↓ signaling
Sympathetic fibers ↑ signaling
Myocardium
④ ↑ Heart rate & contractility Vasoconstriction

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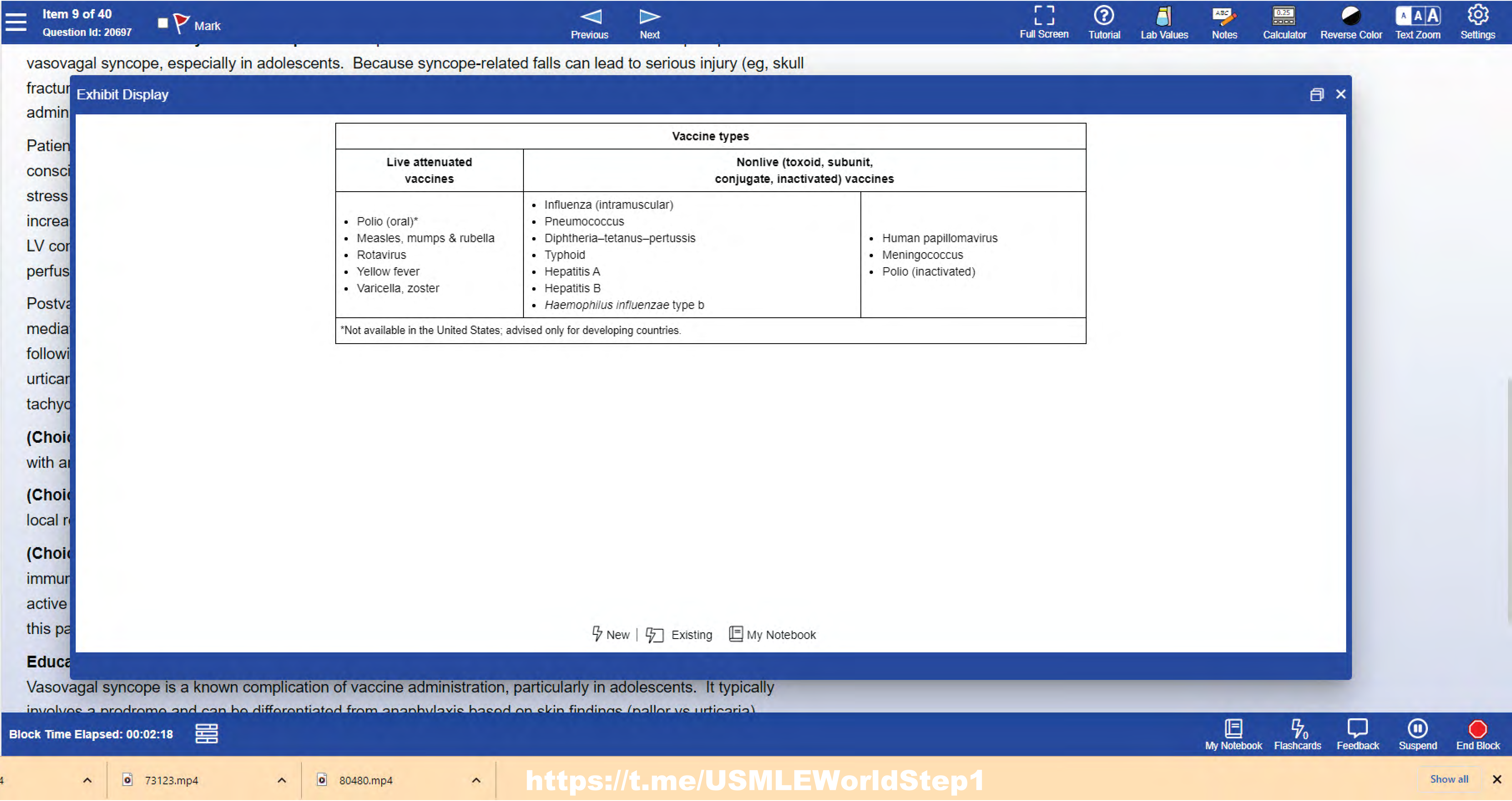
https://t.me/USMLEWorldStep1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vasovagal syncope, especially in adolescents. Because syncope-related falls can lead to serious injury (eg, skull

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Vasovagal syncope is a known complication of vaccine administration, particularly in adolescents. It typically involves a prodrome and can be differentiated from anaphylaxis based on skin findings (pallor vs urticaria).

Exhibit Display

Vaccine types		
Live attenuated vaccines	**Nonlive (toxoid, subunit, conjugate, inactivated) vaccines**	
• Polio (oral)* • Measles, mumps & rubella • Rotavirus • Yellow fever • Varicella, zoster	• Influenza (intramuscular) • Pneumococcus • Diphtheria–tetanus–pertussis • Typhoid • Hepatitis A • Hepatitis B • *Haemophilus influenzae* type b	• Human papillomavirus • Meningococcus • Polio (inactivated)

*Not available in the United States; advised only for developing countries.

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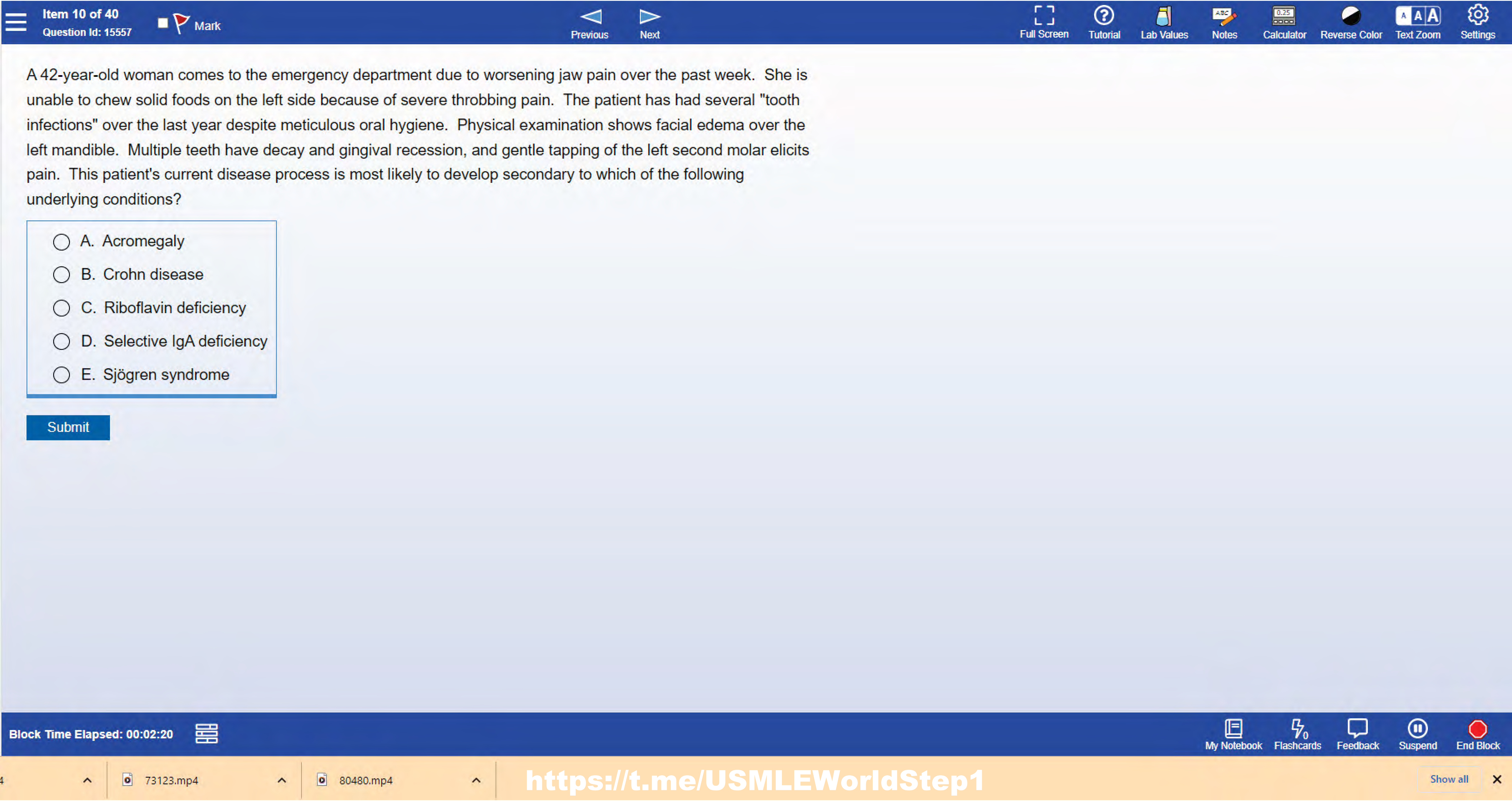
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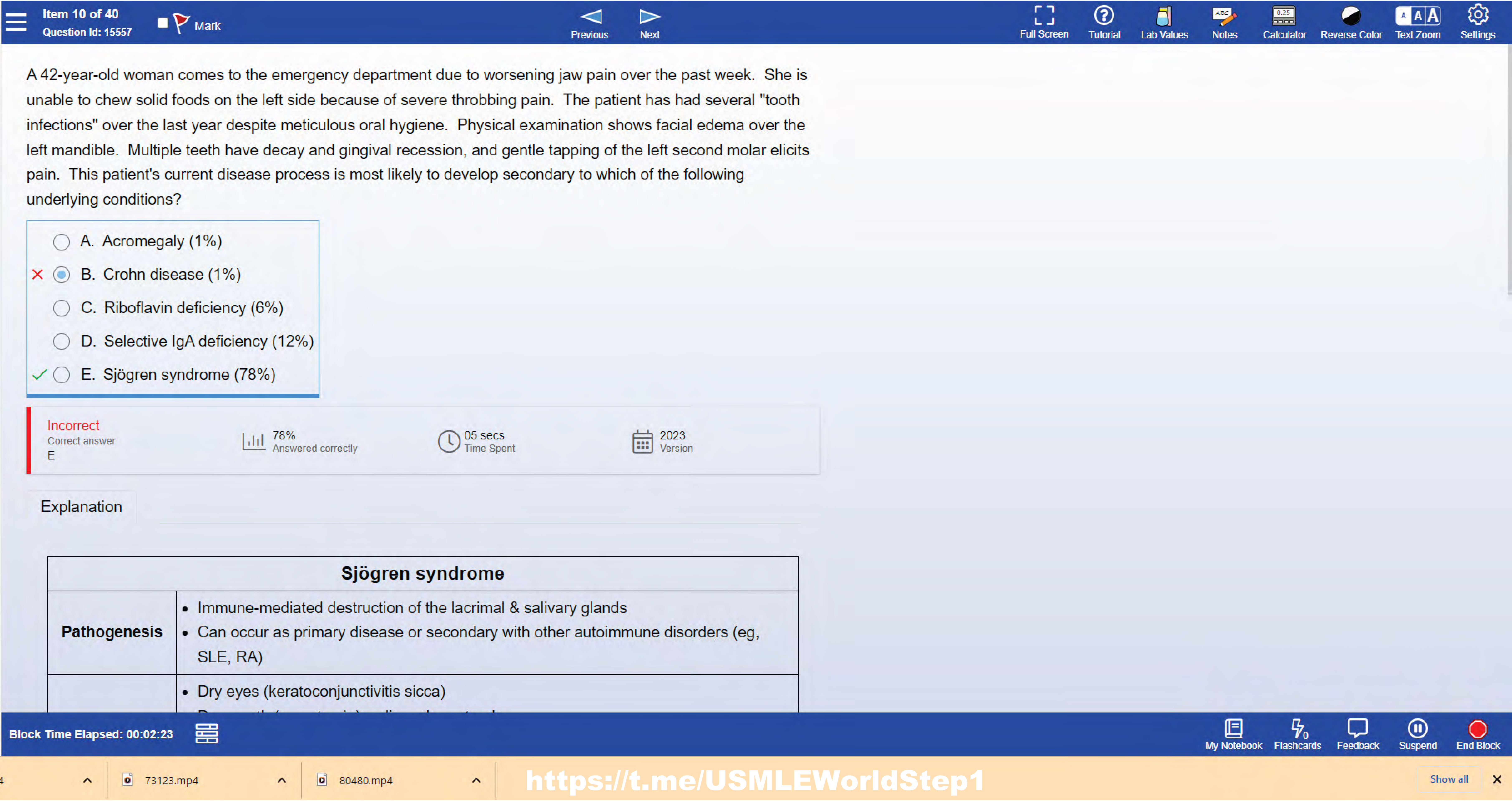
A 42-year-old woman comes to the emergency department due to worsening jaw pain over the past week. She is unable to chew solid foods on the left side because of severe throbbing pain. The patient has had several "tooth infections" over the last year despite meticulous oral hygiene. Physical examination shows facial edema over the left mandible. Multiple teeth have decay and gingival recession, and gentle tapping of the left second molar elicits pain. This patient's current disease process is most likely to develop secondary to which of the following underlying conditions?

- ○ A. Acromegaly
- ○ B. Crohn disease
- ○ C. Riboflavin deficiency
- ○ D. Selective IgA deficiency
- ○ E. Sjögren syndrome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○ A. Acromegaly (1%)
✗ ● B. Crohn disease (1%)
○ C. Riboflavin deficiency (6%)
○ D. Selective IgA deficiency (12%)
✓ ○ E. Sjögren syndrome (78%)

Incorrect
Correct answer
E

78%
Answered correctly

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Explanation

Sjögren syndrome	
Pathogenesis	• Immune-mediated destruction of the lacrimal & salivary glands • Can occur as primary disease or secondary with other autoimmune disorders (eg, SLE, RA)
	• Dry eyes (keratoconjunctivitis sicca)

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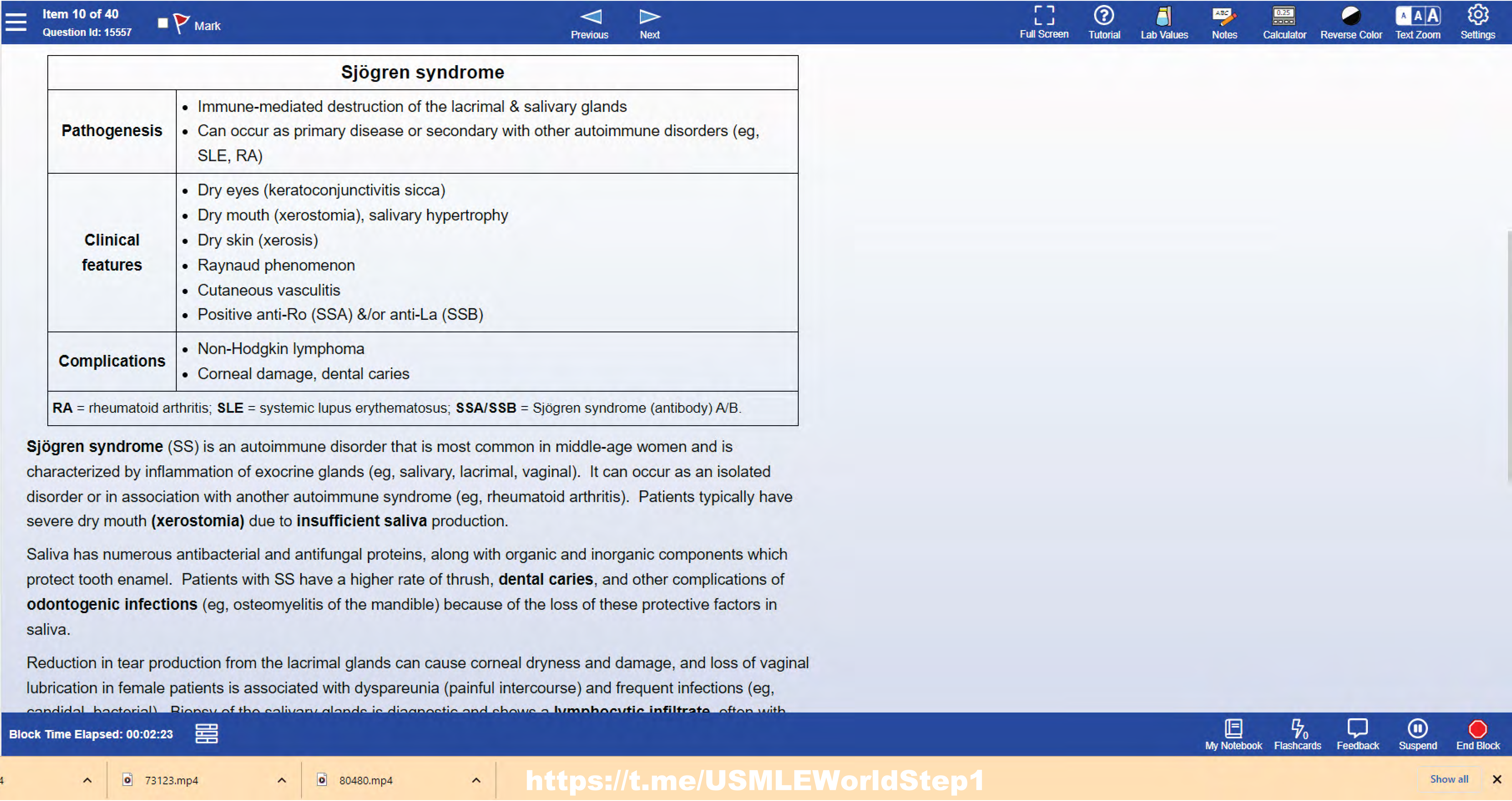

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Sjögren syndrome	
Pathogenesis	• Immune-mediated destruction of the lacrimal & salivary glands • Can occur as primary disease or secondary with other autoimmune disorders (eg, SLE, RA)
Clinical features	• Dry eyes (keratoconjunctivitis sicca) • Dry mouth (xerostomia), salivary hypertrophy • Dry skin (xerosis) • Raynaud phenomenon • Cutaneous vasculitis • Positive anti-Ro (SSA) &/or anti-La (SSB)
Complications	• Non-Hodgkin lymphoma • Corneal damage, dental caries

RA = rheumatoid arthritis; **SLE** = systemic lupus erythematosus; **SSA/SSB** = Sjögren syndrome (antibody) A/B.

Sjögren syndrome (SS) is an autoimmune disorder that is most common in middle-age women and is characterized by inflammation of exocrine glands (eg, salivary, lacrimal, vaginal). It can occur as an isolated disorder or in association with another autoimmune syndrome (eg, rheumatoid arthritis). Patients typically have severe dry mouth **(xerostomia)** due to **insufficient saliva** production.

Saliva has numerous antibacterial and antifungal proteins, along with organic and inorganic components which protect tooth enamel. Patients with SS have a higher rate of thrush, **dental caries**, and other complications of **odontogenic infections** (eg, osteomyelitis of the mandible) because of the loss of these protective factors in saliva.

Reduction in tear production from the lacrimal glands can cause corneal dryness and damage, and loss of vaginal lubrication in female patients is associated with dyspareunia (painful intercourse) and frequent infections (eg, candidal, bacterial). Biopsy of the salivary glands is diagnostic and shows a **lymphocytic infiltrate**, often with

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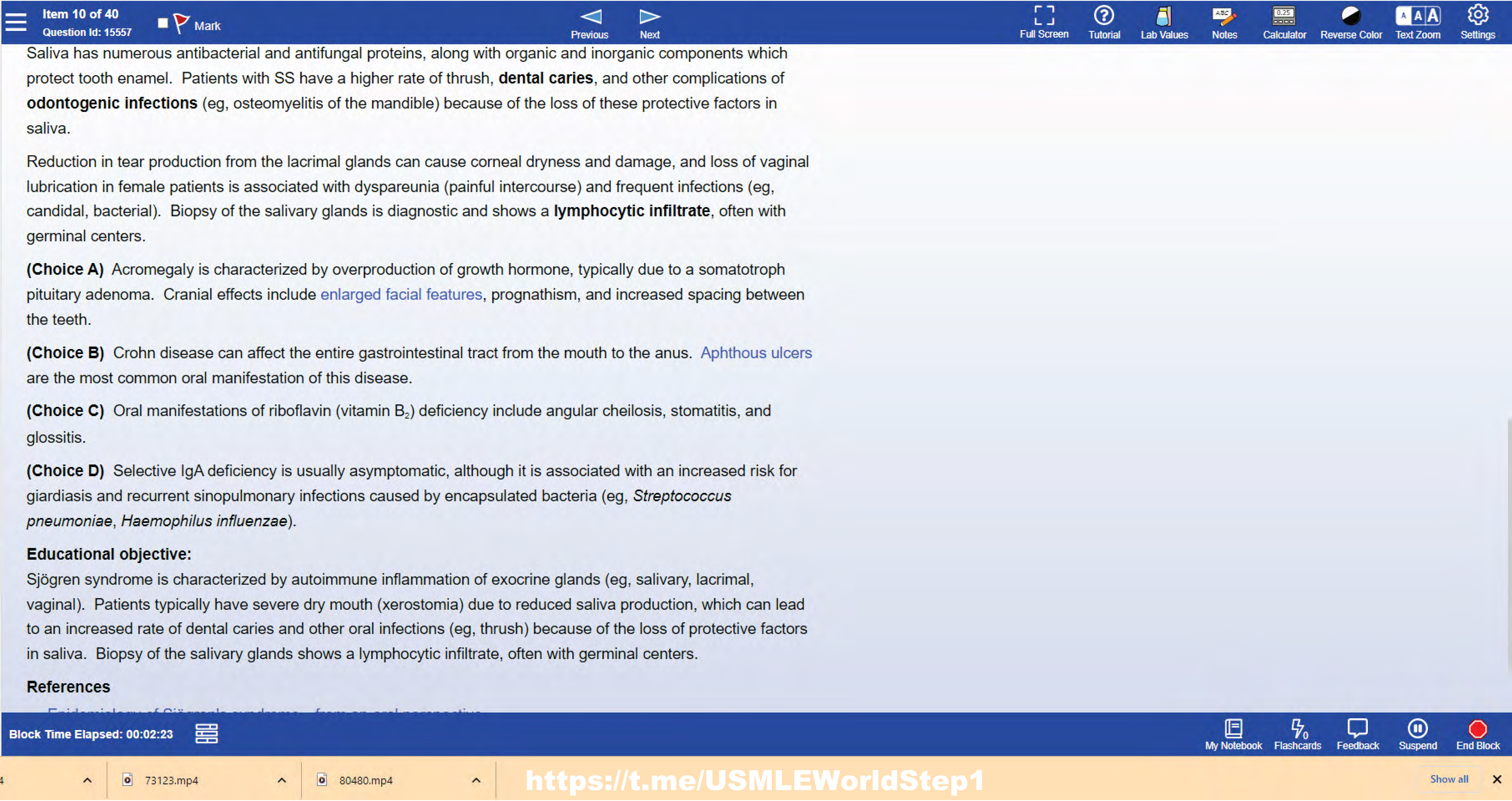
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Reduction in tear production from the lacrimal glands can cause corneal dryness and damage, and loss of vaginal lubrication in female patients is associated with dyspareunia (painful intercourse) and frequent infections (eg, candidal, bacterial). Biopsy of the salivary glands is diagnostic and shows a **lymphocytic infiltrate**, often with germinal centers.

(Choice A) Acromegaly is characterized by overproduction of growth hormone, typically due to a somatotroph pituitary adenoma. Cranial effects include enlarged facial features, prognathism, and increased spacing between the teeth.

(Choice B) Crohn disease can affect the entire gastrointestinal tract from the mouth to the anus. Aphthous ulcers are the most common oral manifestation of this disease.

(Choice C) Oral manifestations of riboflavin (vitamin B_2) deficiency include angular cheilosis, stomatitis, and glossitis.

(Choice D) Selective IgA deficiency is usually asymptomatic, although it is associated with an increased risk for giardiasis and recurrent sinopulmonary infections caused by encapsulated bacteria (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*).

Educational objective:

Sjögren syndrome is characterized by autoimmune inflammation of exocrine glands (eg, salivary, lacrimal, vaginal). Patients typically have severe dry mouth (xerostomia) due to reduced saliva production, which can lead to an increased rate of dental caries and other oral infections (eg, thrush) because of the loss of protective factors in saliva. Biopsy of the salivary glands shows a lymphocytic infiltrate, often with germinal centers.

References

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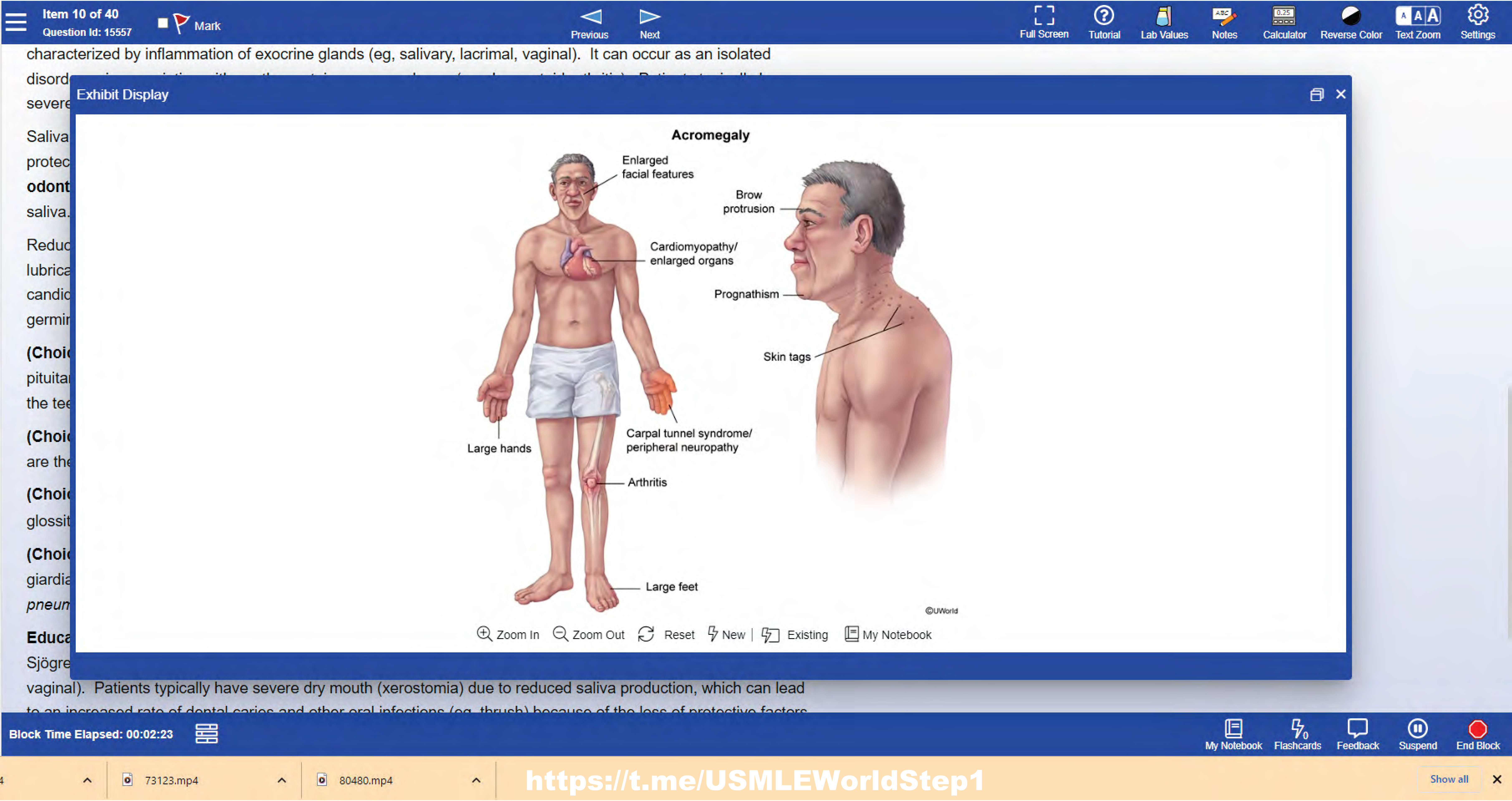
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Acromegaly
Enlarged facial features
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Cardiomyopathy/ enlarged organs
Prognathism
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Carpal tunnel syndrome/ peripheral neuropathy
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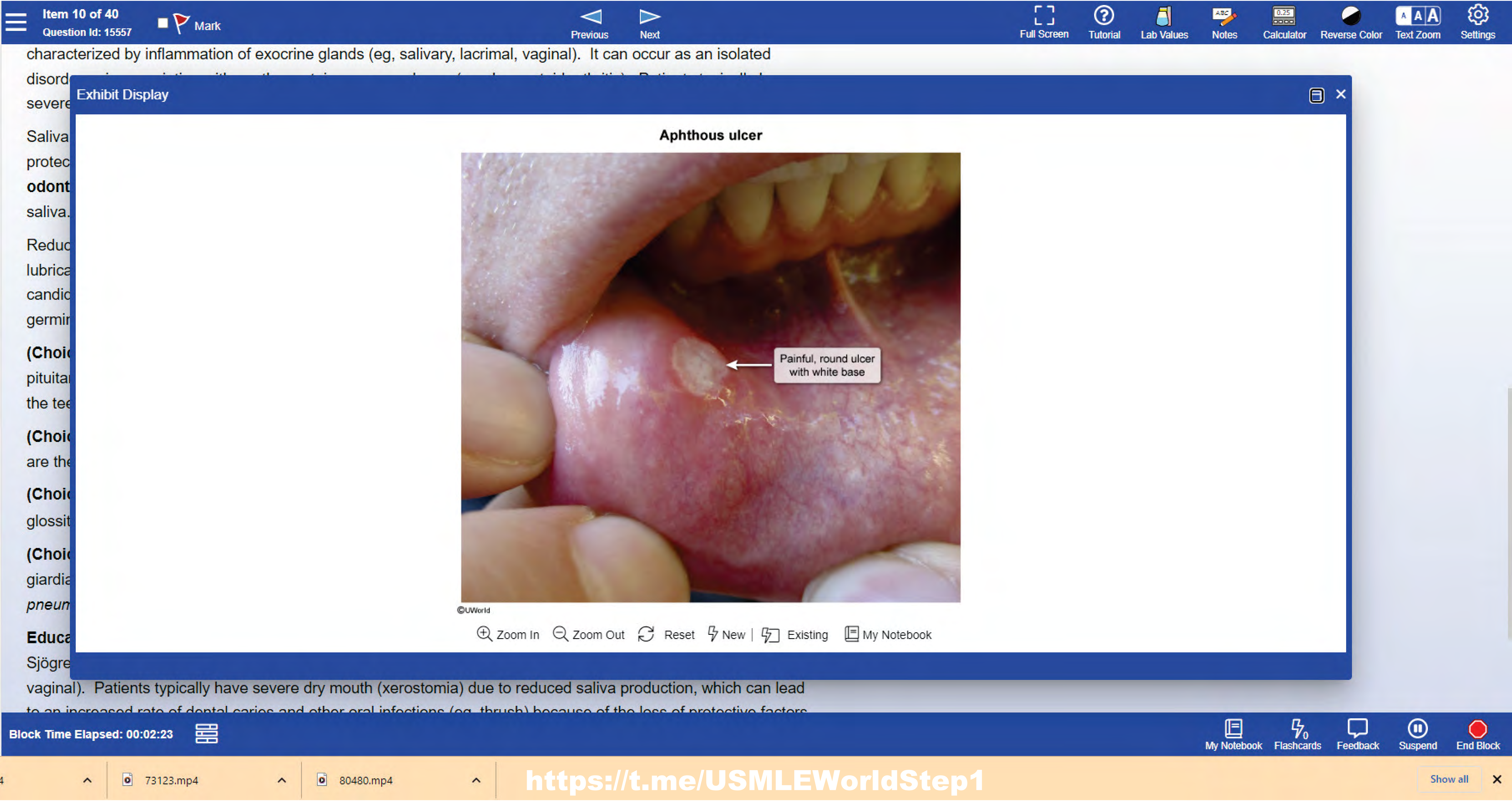
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Aphthous ulcer

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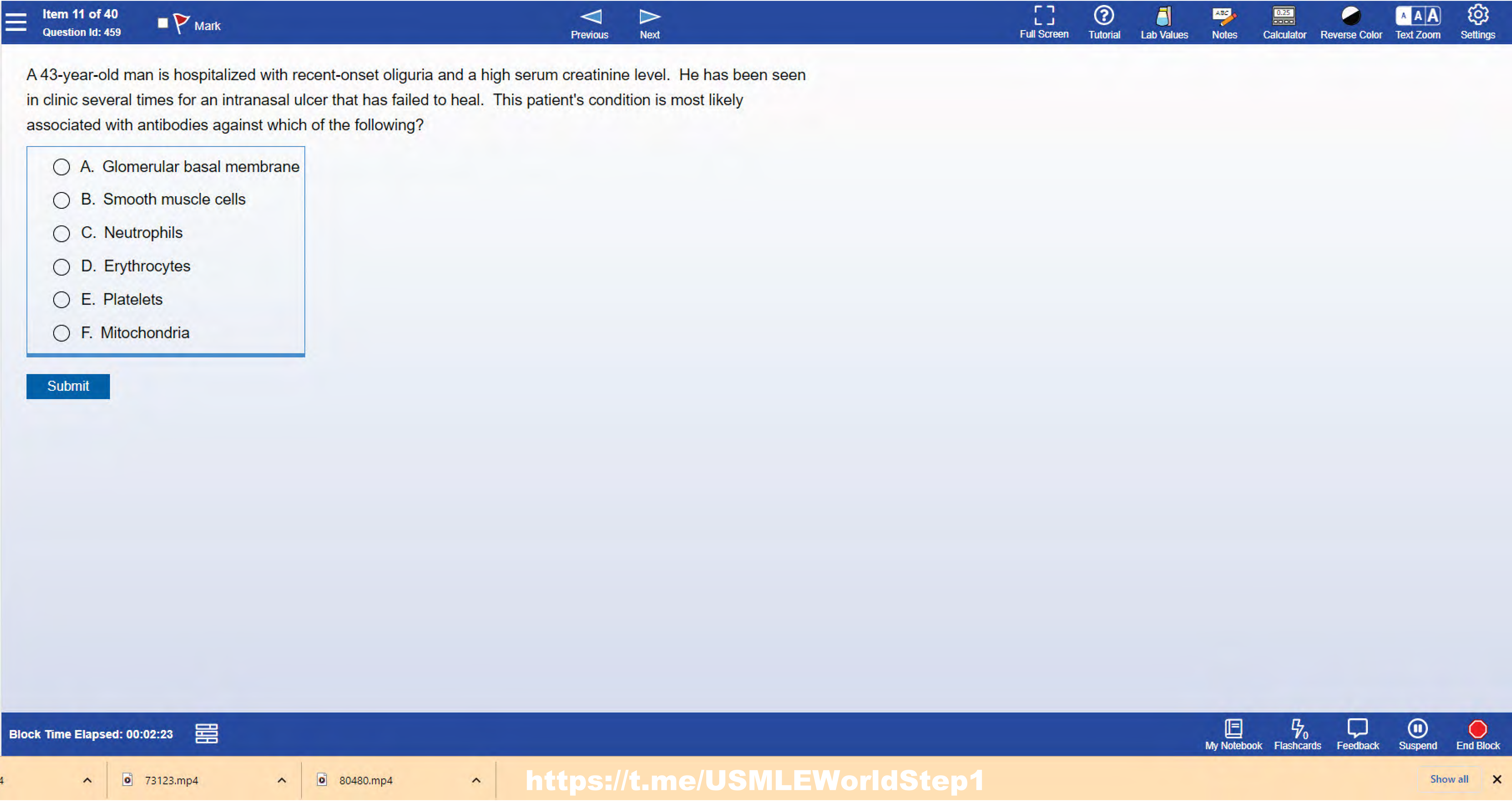
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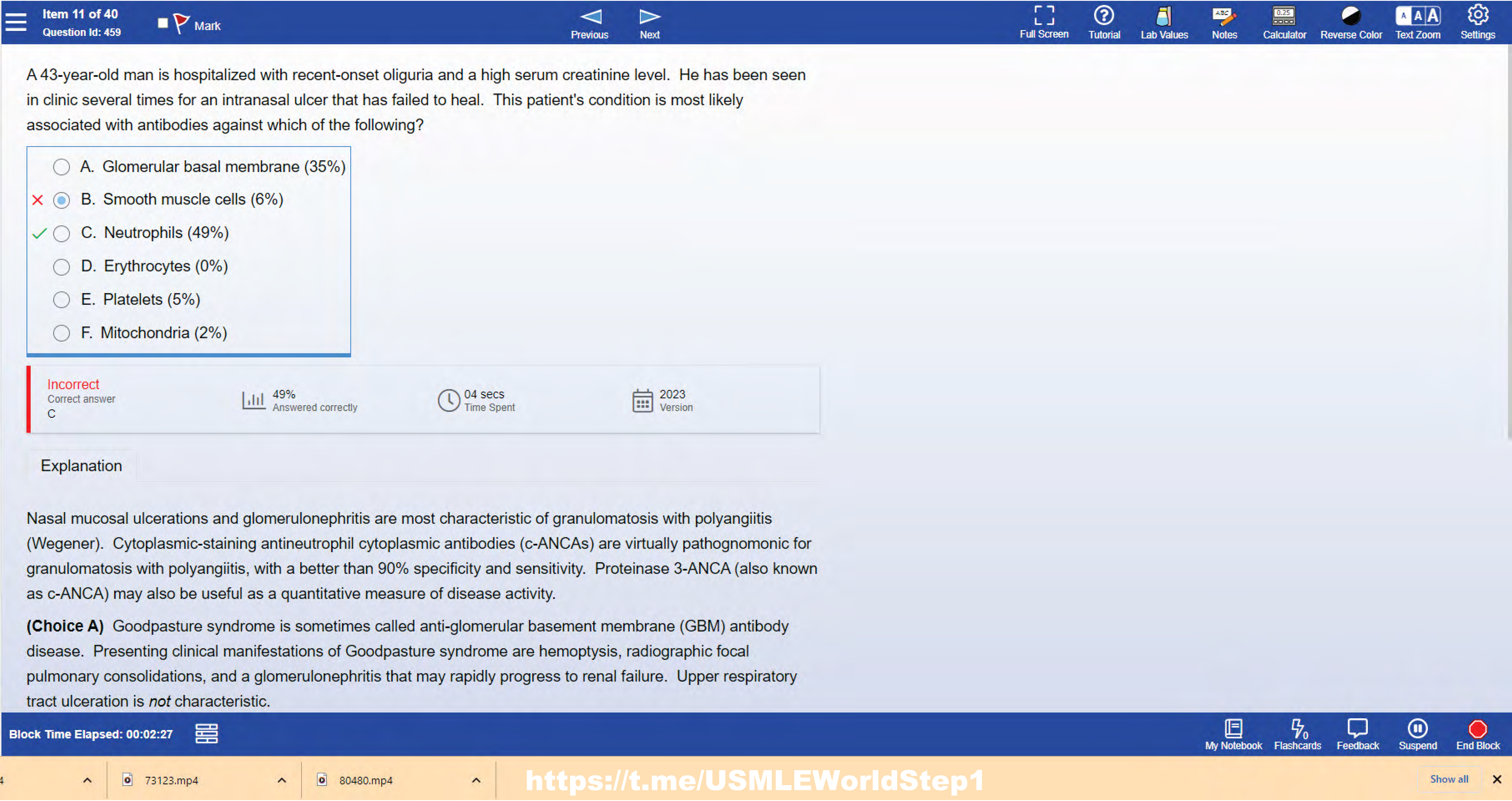
A 43-year-old man is hospitalized with recent-onset oliguria and a high serum creatinine level. He has been seen in clinic several times for an intranasal ulcer that has failed to heal. This patient's condition is most likely associated with antibodies against which of the following?

○ A. Glomerular basal membrane
○ B. Smooth muscle cells
○ C. Neutrophils
○ D. Erythrocytes
○ E. Platelets
○ F. Mitochondria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○ A. Glomerular basal membrane (35%)
✗ ● B. Smooth muscle cells (6%)
✓ ○ C. Neutrophils (49%)
○ D. Erythrocytes (0%)
○ E. Platelets (5%)
○ F. Mitochondria (2%)

Incorrect
Correct answer
C

49%
Answered correctly

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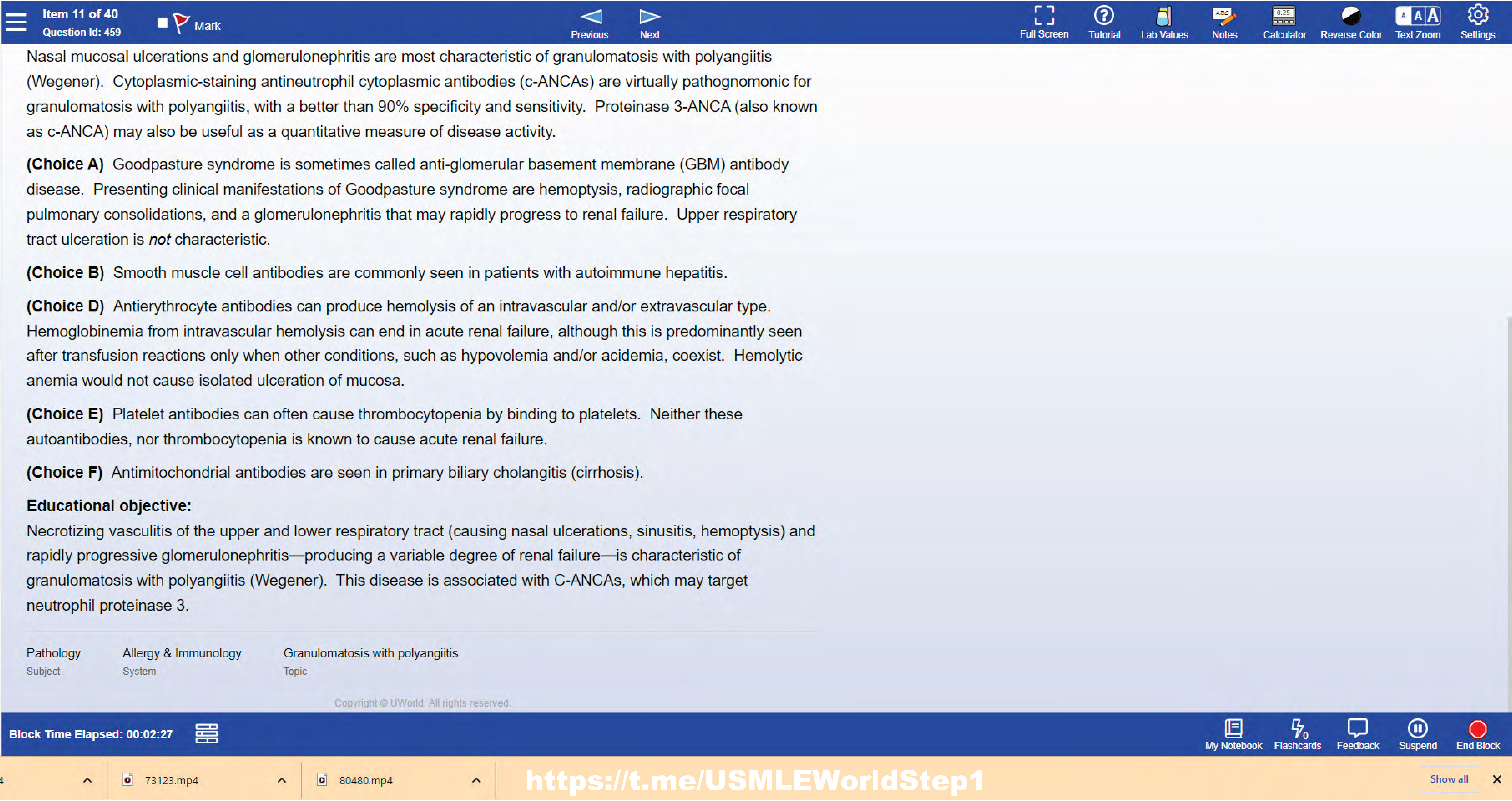
Explanation

Nasal mucosal ulcerations and glomerulonephritis are most characteristic of granulomatosis with polyangiitis (Wegener). Cytoplasmic-staining antineutrophil cytoplasmic antibodies (c-ANCAs) are virtually pathognomonic for granulomatosis with polyangiitis, with a better than 90% specificity and sensitivity. Proteinase 3-ANCA (also known as c-ANCA) may also be useful as a quantitative measure of disease activity.

(Choice A) Goodpasture syndrome is sometimes called anti-glomerular basement membrane (GBM) antibody disease. Presenting clinical manifestations of Goodpasture syndrome are hemoptysis, radiographic focal pulmonary consolidations, and a glomerulonephritis that may rapidly progress to renal failure. Upper respiratory tract ulceration is *not* characteristic.



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(Choice B) Smooth muscle cell antibodies are commonly seen in patients with autoimmune hepatitis.

(Choice D) Antierythrocyte antibodies can produce hemolysis of an intravascular and/or extravascular type. Hemoglobinemia from intravascular hemolysis can end in acute renal failure, although this is predominantly seen after transfusion reactions only when other conditions, such as hypovolemia and/or acidemia, coexist. Hemolytic anemia would not cause isolated ulceration of mucosa.

(Choice E) Platelet antibodies can often cause thrombocytopenia by binding to platelets. Neither these autoantibodies, nor thrombocytopenia is known to cause acute renal failure.

(Choice F) Antimitochondrial antibodies are seen in primary biliary cholangitis (cirrhosis).

Educational objective:
Necrotizing vasculitis of the upper and lower respiratory tract (causing nasal ulcerations, sinusitis, hemoptysis) and rapidly progressive glomerulonephritis—producing a variable degree of renal failure—is characteristic of granulomatosis with polyangiitis (Wegener). This disease is associated with C-ANCAs, which may target neutrophil proteinase 3.

Pathology	Allergy & Immunology	Granulomatosis with polyangiitis
Subject	System	Topic

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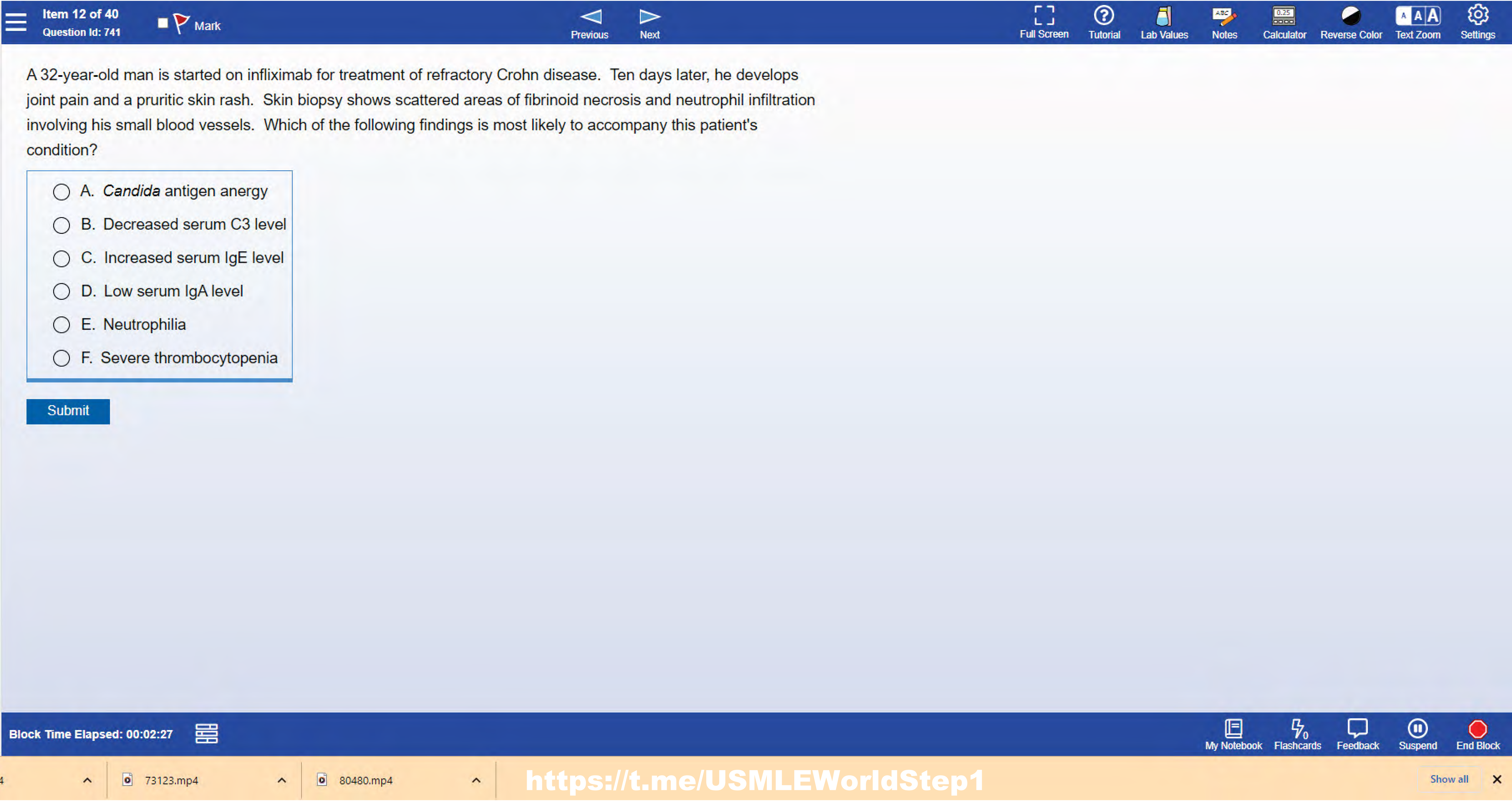
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A 32-year-old man is started on infliximab for treatment of refractory Crohn disease. Ten days later, he develops joint pain and a pruritic skin rash. Skin biopsy shows scattered areas of fibrinoid necrosis and neutrophil infiltration involving his small blood vessels. Which of the following findings is most likely to accompany this patient's condition?

- ○ A. *Candida* antigen anergy
- ○ B. Decreased serum C3 level
- ○ C. Increased serum IgE level
- ○ D. Low serum IgA level
- ○ E. Neutrophilia
- ○ F. Severe thrombocytopenia

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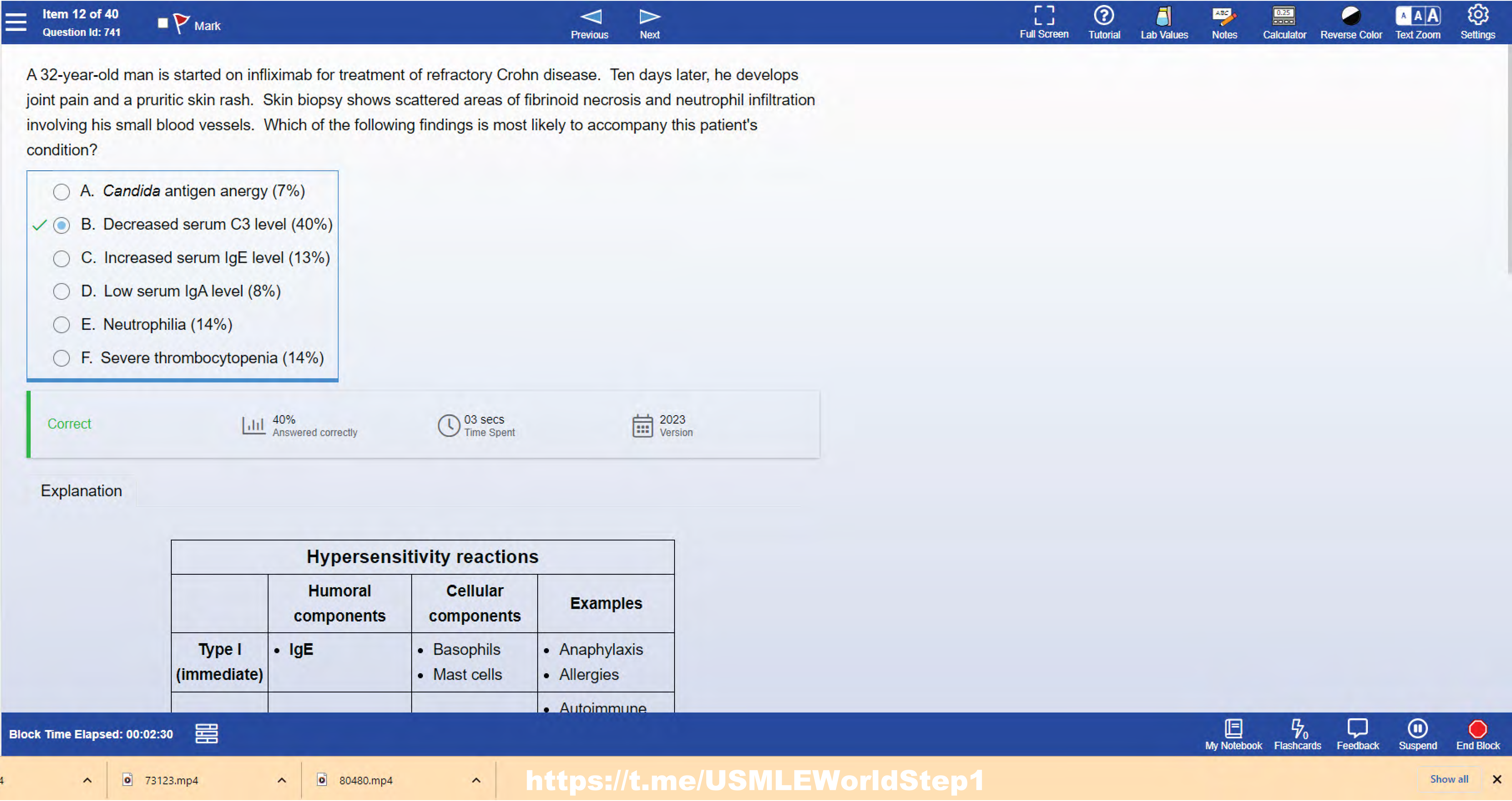
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A 32-year-old man is started on infliximab for treatment of refractory Crohn disease. Ten days later, he develops joint pain and a pruritic skin rash. Skin biopsy shows scattered areas of fibrinoid necrosis and neutrophil infiltration involving his small blood vessels. Which of the following findings is most likely to accompany this patient's condition?

- ○ A. *Candida* antigen anergy (7%)
- ✓ ● B. Decreased serum C3 level (40%)
- ○ C. Increased serum IgE level (13%)
- ○ D. Low serum IgA level (8%)
- ○ E. Neutrophilia (14%)
- ○ F. Severe thrombocytopenia (14%)

Correct

40%
Answered correctly

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Explanation

Hypersensitivity reactions			
	Humoral components	**Cellular components**	**Examples**
Type I (immediate)	• **IgE**	• Basophils • Mast cells	• Anaphylaxis • Allergies
			• Autoimmune

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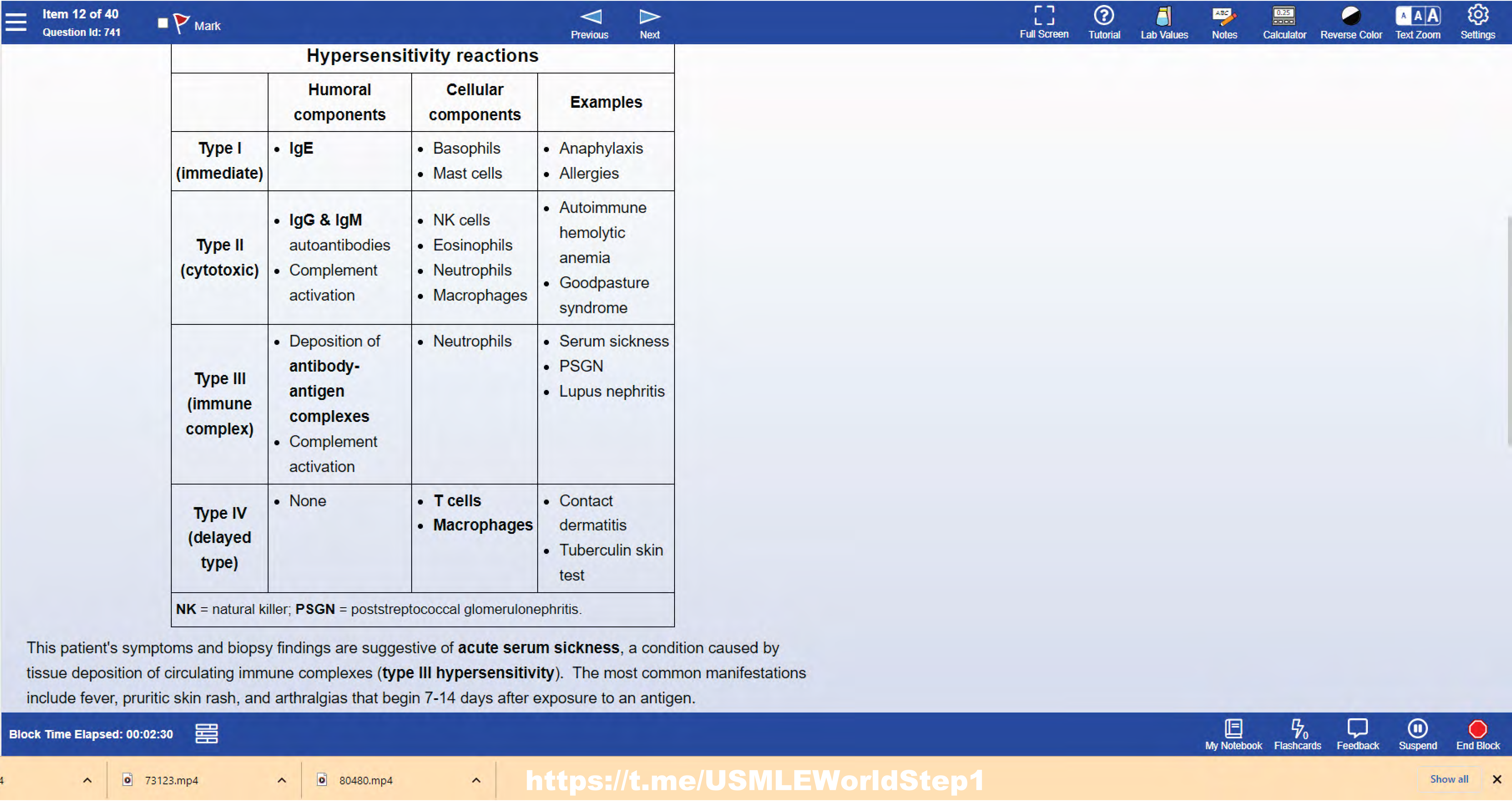
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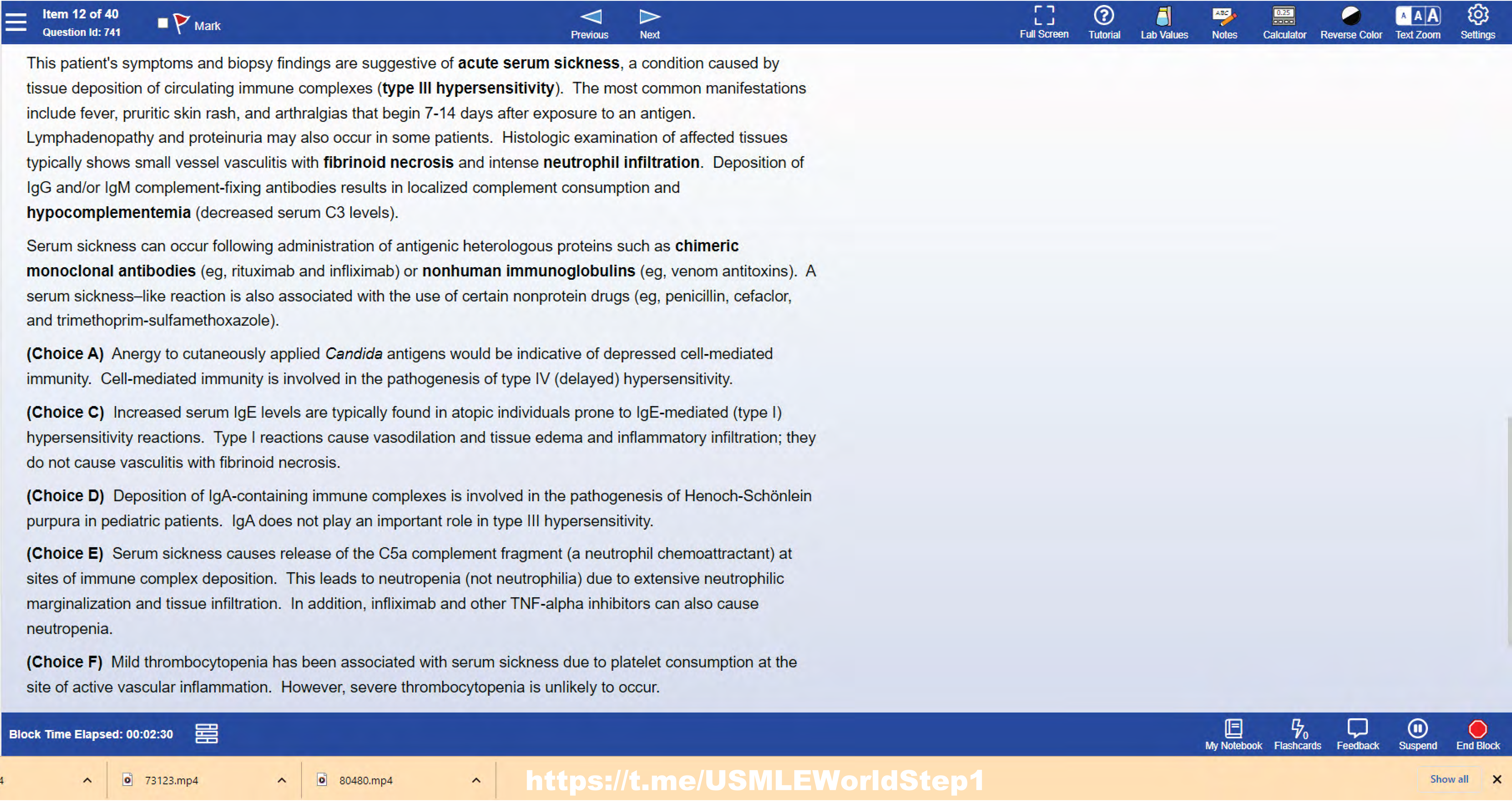
Hypersensitivity reactions

	Humoral components	Cellular components	Examples
Type I (immediate)	• **IgE**	• Basophils • Mast cells	• Anaphylaxis • Allergies
Type II (cytotoxic)	• **IgG & IgM** autoantibodies • Complement activation	• NK cells • Eosinophils • Neutrophils • Macrophages	• Autoimmune hemolytic anemia • Goodpasture syndrome
Type III (immune complex)	• Deposition of **antibody-antigen complexes** • Complement activation	• Neutrophils	• Serum sickness • PSGN • Lupus nephritis
Type IV (delayed type)	• None	• **T cells** • **Macrophages**	• Contact dermatitis • Tuberculin skin test

NK = natural killer; **PSGN** = poststreptococcal glomerulonephritis.

This patient's symptoms and biopsy findings are suggestive of **acute serum sickness**, a condition caused by tissue deposition of circulating immune complexes (**type III hypersensitivity**). The most common manifestations include fever, pruritic skin rash, and arthralgias that begin 7-14 days after exposure to an antigen.



This patient's symptoms and biopsy findings are suggestive of **acute serum sickness**, a condition caused by tissue deposition of circulating immune complexes (**type III hypersensitivity**). The most common manifestations include fever, pruritic skin rash, and arthralgias that begin 7-14 days after exposure to an antigen. Lymphadenopathy and proteinuria may also occur in some patients. Histologic examination of affected tissues typically shows small vessel vasculitis with **fibrinoid necrosis** and intense **neutrophil infiltration**. Deposition of IgG and/or IgM complement-fixing antibodies results in localized complement consumption and **hypocomplementemia** (decreased serum C3 levels).

Serum sickness can occur following administration of antigenic heterologous proteins such as **chimeric monoclonal antibodies** (eg, rituximab and infliximab) or **nonhuman immunoglobulins** (eg, venom antitoxins). A serum sickness–like reaction is also associated with the use of certain nonprotein drugs (eg, penicillin, cefaclor, and trimethoprim-sulfamethoxazole).

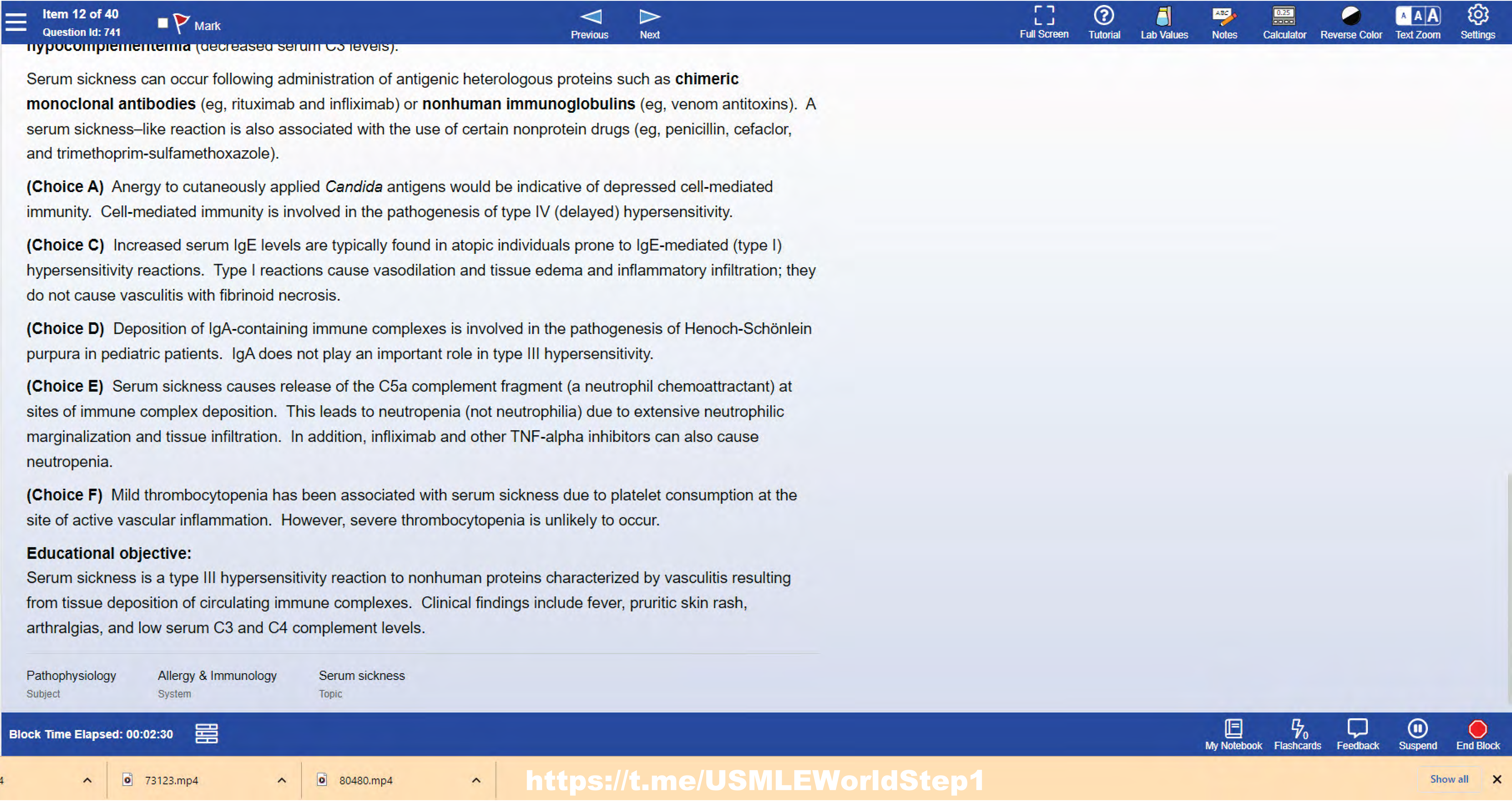
(Choice A) Anergy to cutaneously applied *Candida* antigens would be indicative of depressed cell-mediated immunity. Cell-mediated immunity is involved in the pathogenesis of type IV (delayed) hypersensitivity.

(Choice C) Increased serum IgE levels are typically found in atopic individuals prone to IgE-mediated (type I) hypersensitivity reactions. Type I reactions cause vasodilation and tissue edema and inflammatory infiltration; they do not cause vasculitis with fibrinoid necrosis.

(Choice D) Deposition of IgA-containing immune complexes is involved in the pathogenesis of Henoch-Schönlein purpura in pediatric patients. IgA does not play an important role in type III hypersensitivity.

(Choice E) Serum sickness causes release of the C5a complement fragment (a neutrophil chemoattractant) at sites of immune complex deposition. This leads to neutropenia (not neutrophilia) due to extensive neutrophilic marginalization and tissue infiltration. In addition, infliximab and other TNF-alpha inhibitors can also cause neutropenia.

(Choice F) Mild thrombocytopenia has been associated with serum sickness due to platelet consumption at the site of active vascular inflammation. However, severe thrombocytopenia is unlikely to occur.



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(Choice F) Mild thrombocytopenia has been associated with serum sickness due to platelet consumption at the site of active vascular inflammation. However, severe thrombocytopenia is unlikely to occur.

Educational objective:
Serum sickness is a type III hypersensitivity reaction to nonhuman proteins characterized by vasculitis resulting from tissue deposition of circulating immune complexes. Clinical findings include fever, pruritic skin rash, arthralgias, and low serum C3 and C4 complement levels.

Pathophysiology	Allergy & Immunology	Serum sickness
Subject	System	Topic

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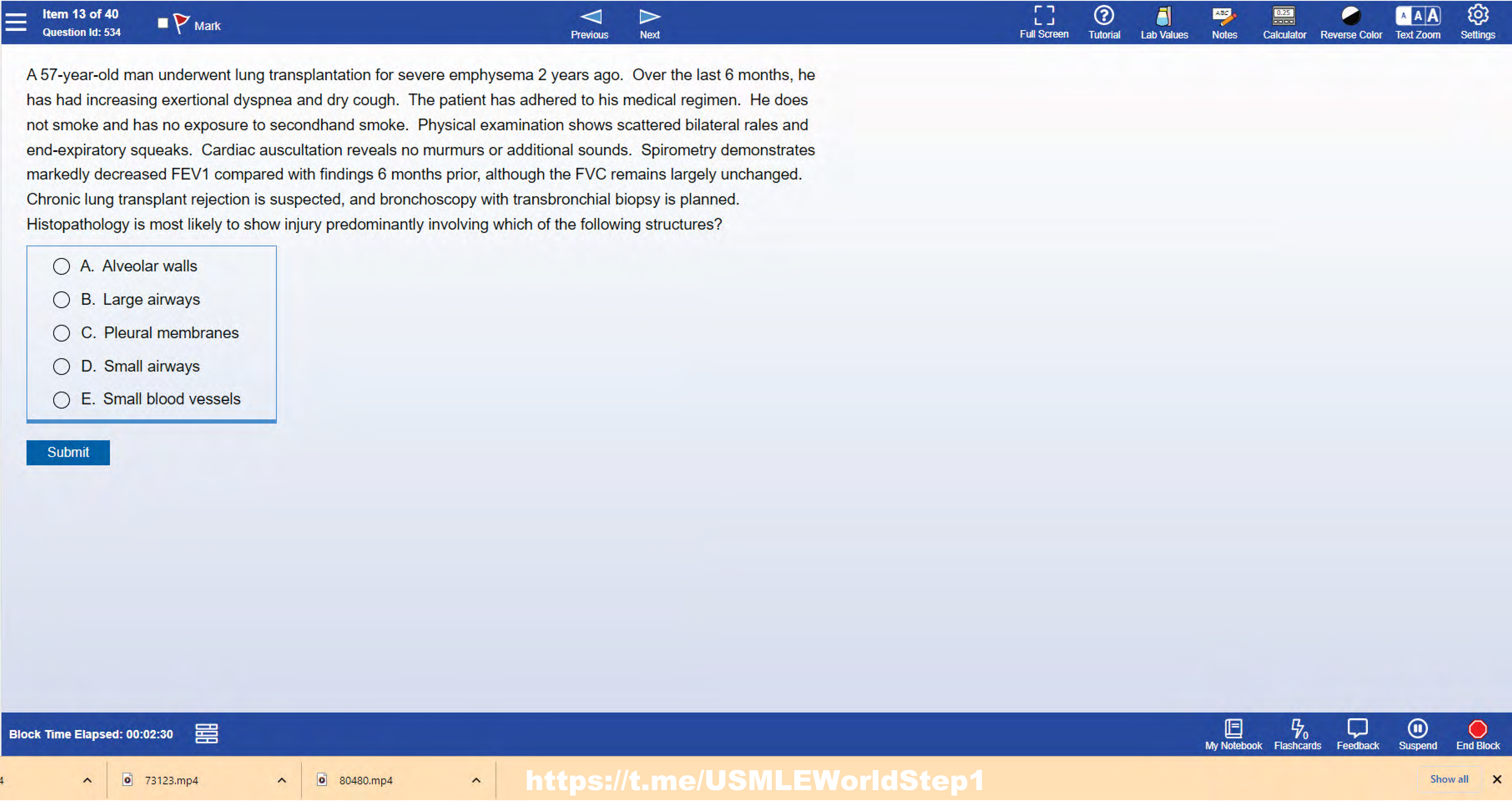
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A 57-year-old man underwent lung transplantation for severe emphysema 2 years ago. Over the last 6 months, he has had increasing exertional dyspnea and dry cough. The patient has adhered to his medical regimen. He does not smoke and has no exposure to secondhand smoke. Physical examination shows scattered bilateral rales and end-expiratory squeaks. Cardiac auscultation reveals no murmurs or additional sounds. Spirometry demonstrates markedly decreased FEV1 compared with findings 6 months prior, although the FVC remains largely unchanged. Chronic lung transplant rejection is suspected, and bronchoscopy with transbronchial biopsy is planned. Histopathology is most likely to show injury predominantly involving which of the following structures?

○ A. Alveolar walls
○ B. Large airways
○ C. Pleural membranes
○ D. Small airways
○ E. Small blood vessels

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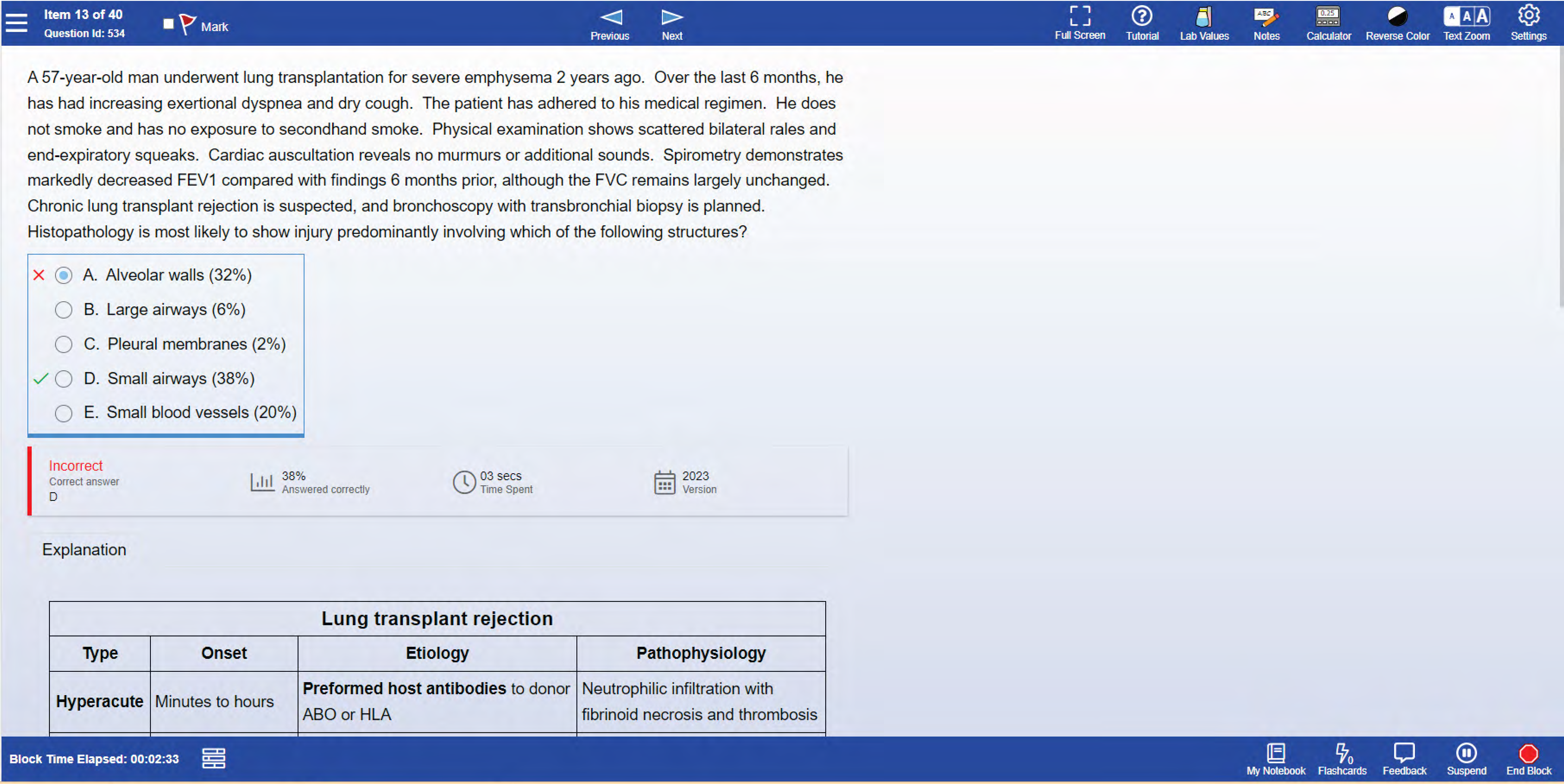
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- ✗ ● A. Alveolar walls (32%)
- ○ B. Large airways (6%)
- ○ C. Pleural membranes (2%)
- ✓ ○ D. Small airways (38%)
- ○ E. Small blood vessels (20%)

Incorrect
Correct answer
D

38%
Answered correctly

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Explanation

Lung transplant rejection			
Type	**Onset**	**Etiology**	**Pathophysiology**
Hyperacute	Minutes to hours	**Preformed host antibodies** to donor ABO or HLA	Neutrophilic infiltration with fibrinoid necrosis and thrombosis

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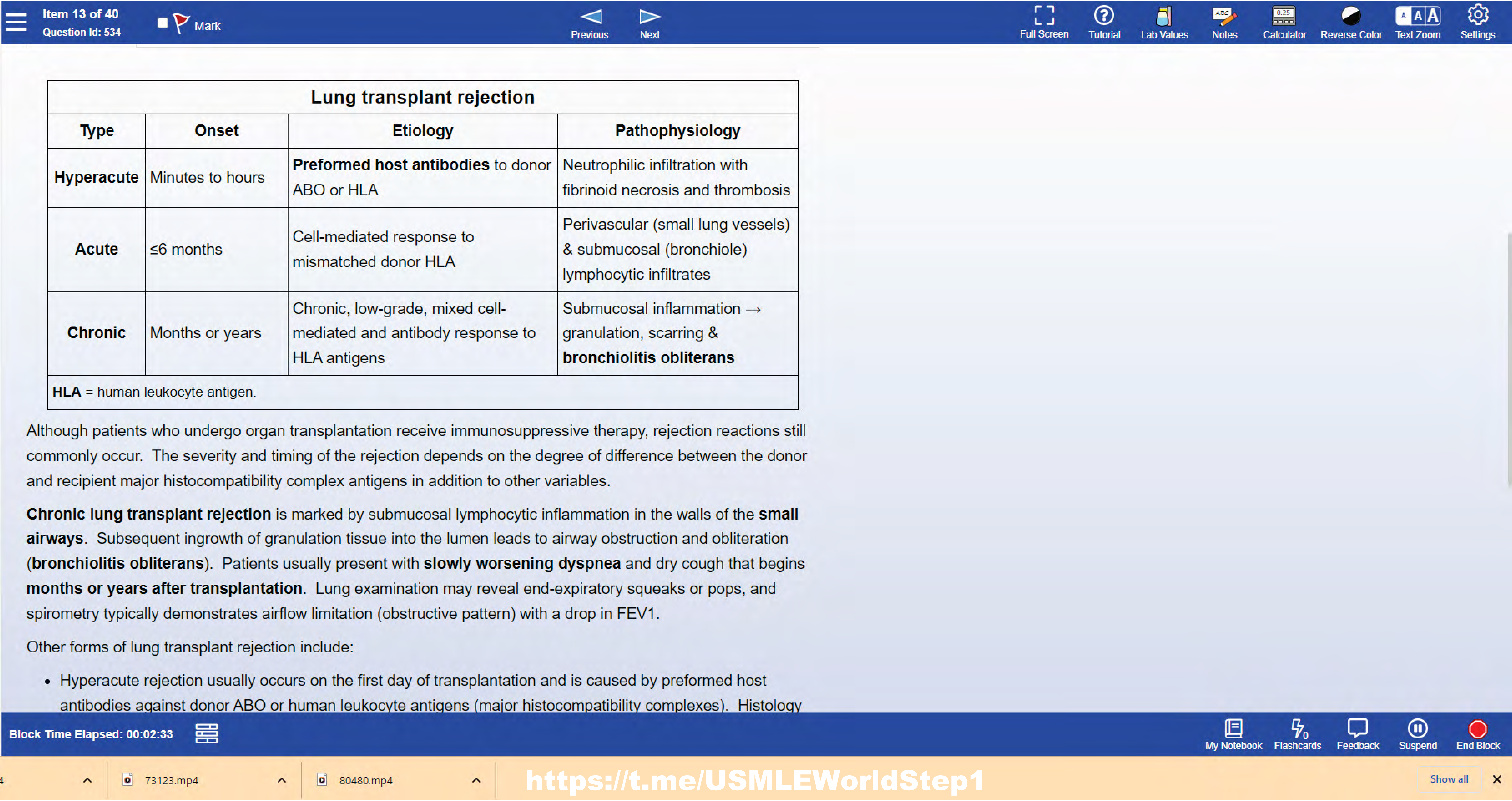
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Lung transplant rejection

Type	Onset	Etiology	Pathophysiology
Hyperacute	Minutes to hours	**Preformed host antibodies** to donor ABO or HLA	Neutrophilic infiltration with fibrinoid necrosis and thrombosis
Acute	≤6 months	Cell-mediated response to mismatched donor HLA	Perivascular (small lung vessels) & submucosal (bronchiole) lymphocytic infiltrates
Chronic	Months or years	Chronic, low-grade, mixed cell-mediated and antibody response to HLA antigens	Submucosal inflammation → granulation, scarring & **bronchiolitis obliterans**

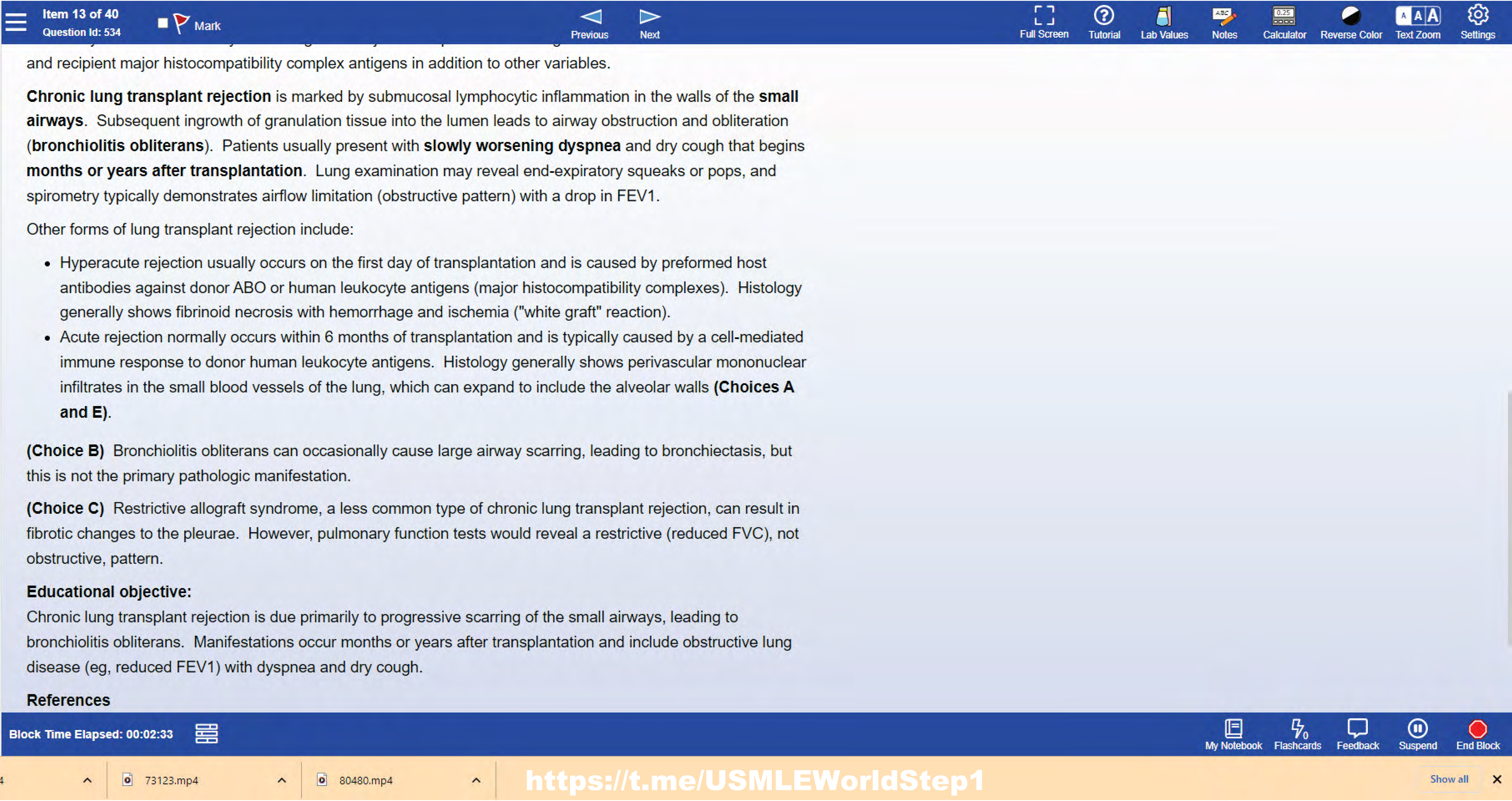
HLA = human leukocyte antigen.

Although patients who undergo organ transplantation receive immunosuppressive therapy, rejection reactions still commonly occur. The severity and timing of the rejection depends on the degree of difference between the donor and recipient major histocompatibility complex antigens in addition to other variables.

Chronic lung transplant rejection is marked by submucosal lymphocytic inflammation in the walls of the **small airways**. Subsequent ingrowth of granulation tissue into the lumen leads to airway obstruction and obliteration (**bronchiolitis obliterans**). Patients usually present with **slowly worsening dyspnea** and dry cough that begins **months or years after transplantation**. Lung examination may reveal end-expiratory squeaks or pops, and spirometry typically demonstrates airflow limitation (obstructive pattern) with a drop in FEV1.

Other forms of lung transplant rejection include:

- Hyperacute rejection usually occurs on the first day of transplantation and is caused by preformed host antibodies against donor ABO or human leukocyte antigens (major histocompatibility complexes). Histology



and recipient major histocompatibility complex antigens in addition to other variables.

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Other forms of lung transplant rejection include:

- Hyperacute rejection usually occurs on the first day of transplantation and is caused by preformed host antibodies against donor ABO or human leukocyte antigens (major histocompatibility complexes). Histology generally shows fibrinoid necrosis with hemorrhage and ischemia ("white graft" reaction).
- Acute rejection normally occurs within 6 months of transplantation and is typically caused by a cell-mediated immune response to donor human leukocyte antigens. Histology generally shows perivascular mononuclear infiltrates in the small blood vessels of the lung, which can expand to include the alveolar walls **(Choices A and E)**.

(Choice B) Bronchiolitis obliterans can occasionally cause large airway scarring, leading to bronchiectasis, but this is not the primary pathologic manifestation.

(Choice C) Restrictive allograft syndrome, a less common type of chronic lung transplant rejection, can result in fibrotic changes to the pleurae. However, pulmonary function tests would reveal a restrictive (reduced FVC), not obstructive, pattern.

Educational objective:
Chronic lung transplant rejection is due primarily to progressive scarring of the small airways, leading to bronchiolitis obliterans. Manifestations occur months or years after transplantation and include obstructive lung disease (eg, reduced FEV1) with dyspnea and dry cough.

References

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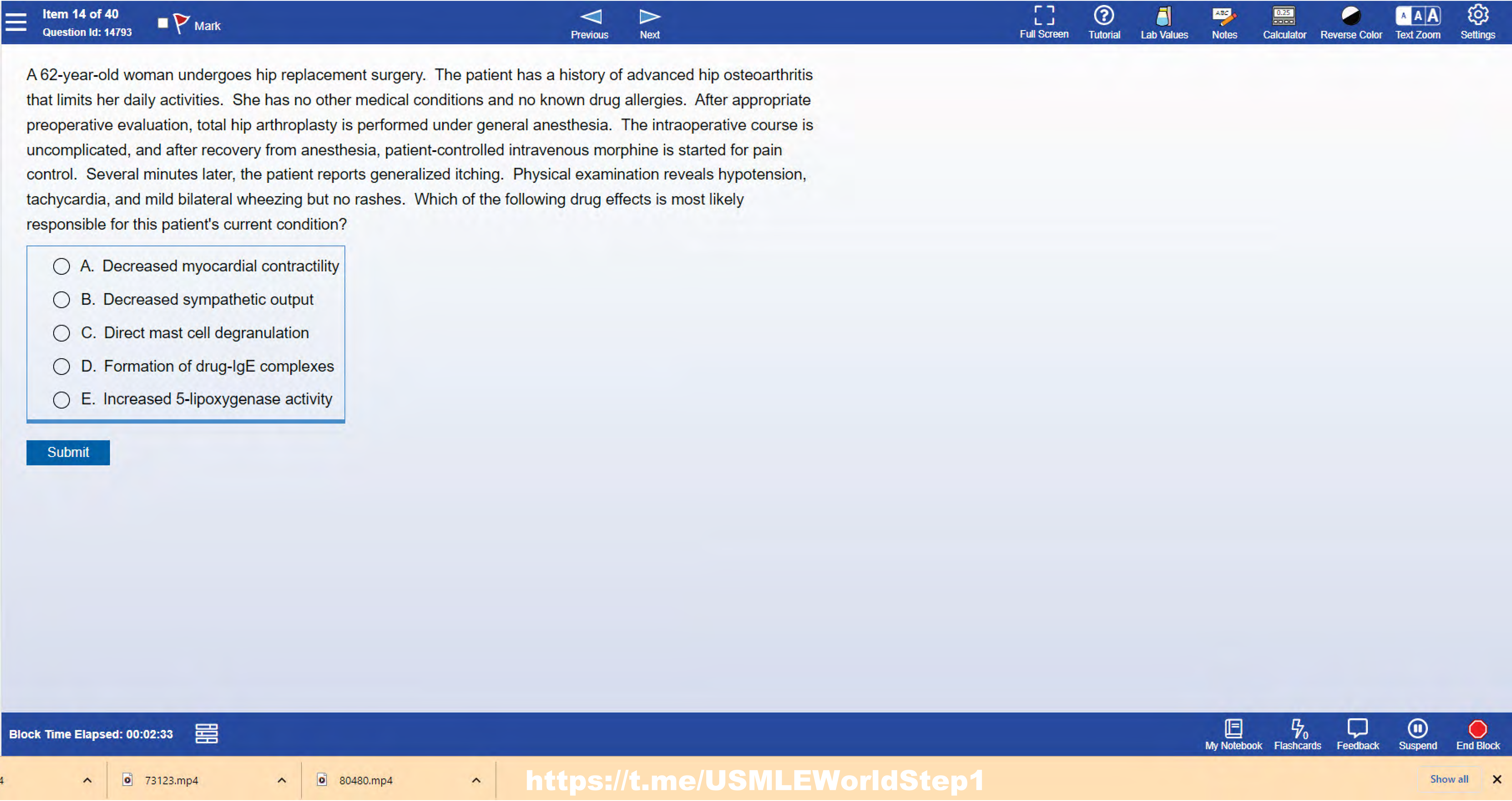
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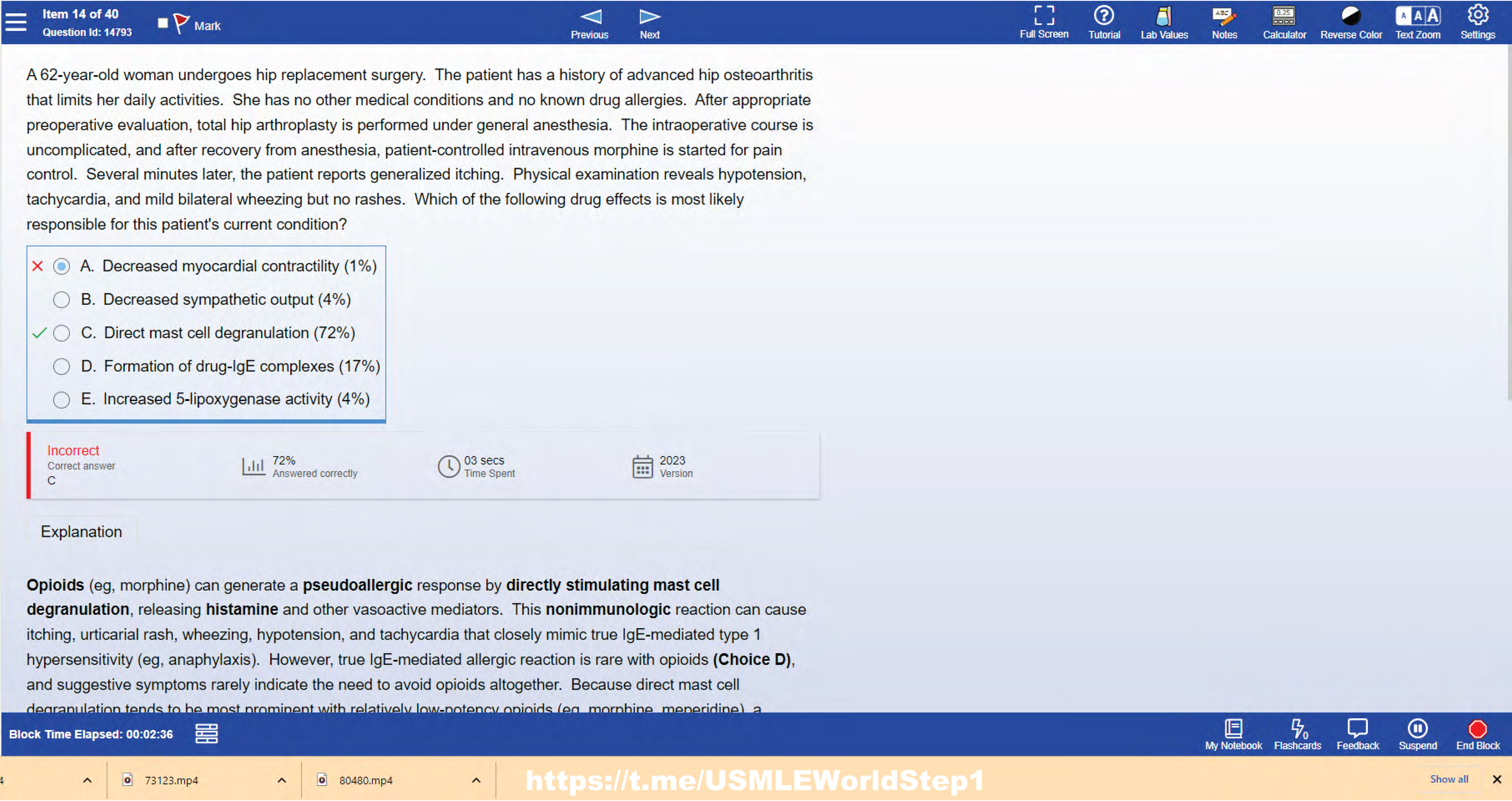
A 62-year-old woman undergoes hip replacement surgery. The patient has a history of advanced hip osteoarthritis that limits her daily activities. She has no other medical conditions and no known drug allergies. After appropriate preoperative evaluation, total hip arthroplasty is performed under general anesthesia. The intraoperative course is uncomplicated, and after recovery from anesthesia, patient-controlled intravenous morphine is started for pain control. Several minutes later, the patient reports generalized itching. Physical examination reveals hypotension, tachycardia, and mild bilateral wheezing but no rashes. Which of the following drug effects is most likely responsible for this patient's current condition?

○ A. Decreased myocardial contractility
○ B. Decreased sympathetic output
○ C. Direct mast cell degranulation
○ D. Formation of drug-IgE complexes
○ E. Increased 5-lipoxygenase activity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- ✗ ● A. Decreased myocardial contractility (1%)
- ○ B. Decreased sympathetic output (4%)
- ✓ ○ C. Direct mast cell degranulation (72%)
- ○ D. Formation of drug-IgE complexes (17%)
- ○ E. Increased 5-lipoxygenase activity (4%)

Incorrect
Correct answer
C

72%
Answered correctly

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Explanation

Opioids (eg, morphine) can generate a **pseudoallergic** response by **directly stimulating mast cell degranulation**, releasing **histamine** and other vasoactive mediators. This **nonimmunologic** reaction can cause itching, urticarial rash, wheezing, hypotension, and tachycardia that closely mimic true IgE-mediated type 1 hypersensitivity (eg, anaphylaxis). However, true IgE-mediated allergic reaction is rare with opioids **(Choice D)**, and suggestive symptoms rarely indicate the need to avoid opioids altogether. Because direct mast cell degranulation tends to be most prominent with relatively low-potency opioids (eg, morphine, meperidine), a

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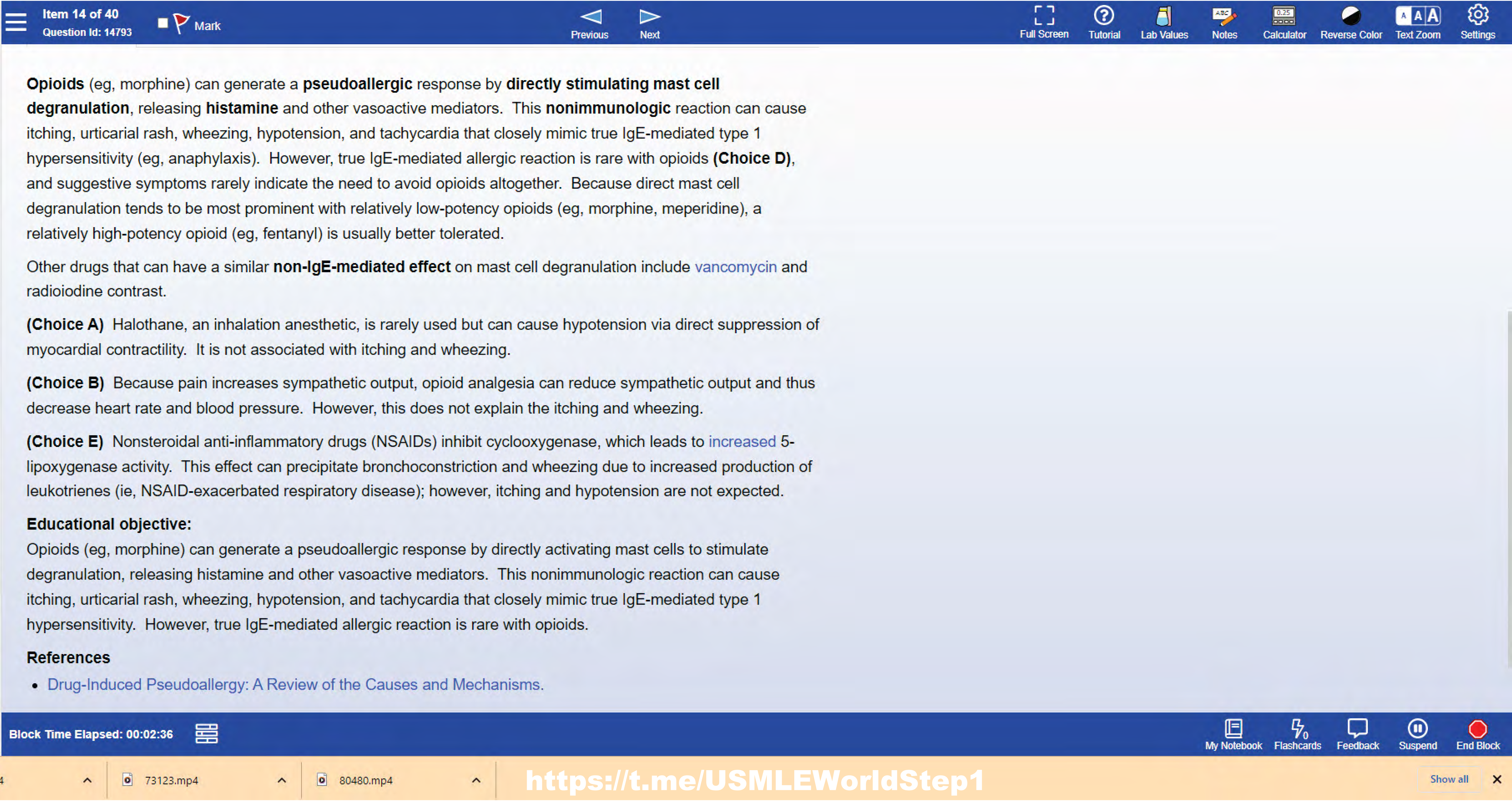
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Other drugs that can have a similar **non-IgE-mediated effect** on mast cell degranulation include vancomycin and radioiodine contrast.

(Choice A) Halothane, an inhalation anesthetic, is rarely used but can cause hypotension via direct suppression of myocardial contractility. It is not associated with itching and wheezing.

(Choice B) Because pain increases sympathetic output, opioid analgesia can reduce sympathetic output and thus decrease heart rate and blood pressure. However, this does not explain the itching and wheezing.

(Choice E) Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase, which leads to increased 5-lipoxygenase activity. This effect can precipitate bronchoconstriction and wheezing due to increased production of leukotrienes (ie, NSAID-exacerbated respiratory disease); however, itching and hypotension are not expected.

Educational objective:

Opioids (eg, morphine) can generate a pseudoallergic response by directly activating mast cells to stimulate degranulation, releasing histamine and other vasoactive mediators. This nonimmunologic reaction can cause itching, urticarial rash, wheezing, hypotension, and tachycardia that closely mimic true IgE-mediated type 1 hypersensitivity. However, true IgE-mediated allergic reaction is rare with opioids.

References

- Drug-Induced Pseudoallergy: A Review of the Causes and Mechanisms.

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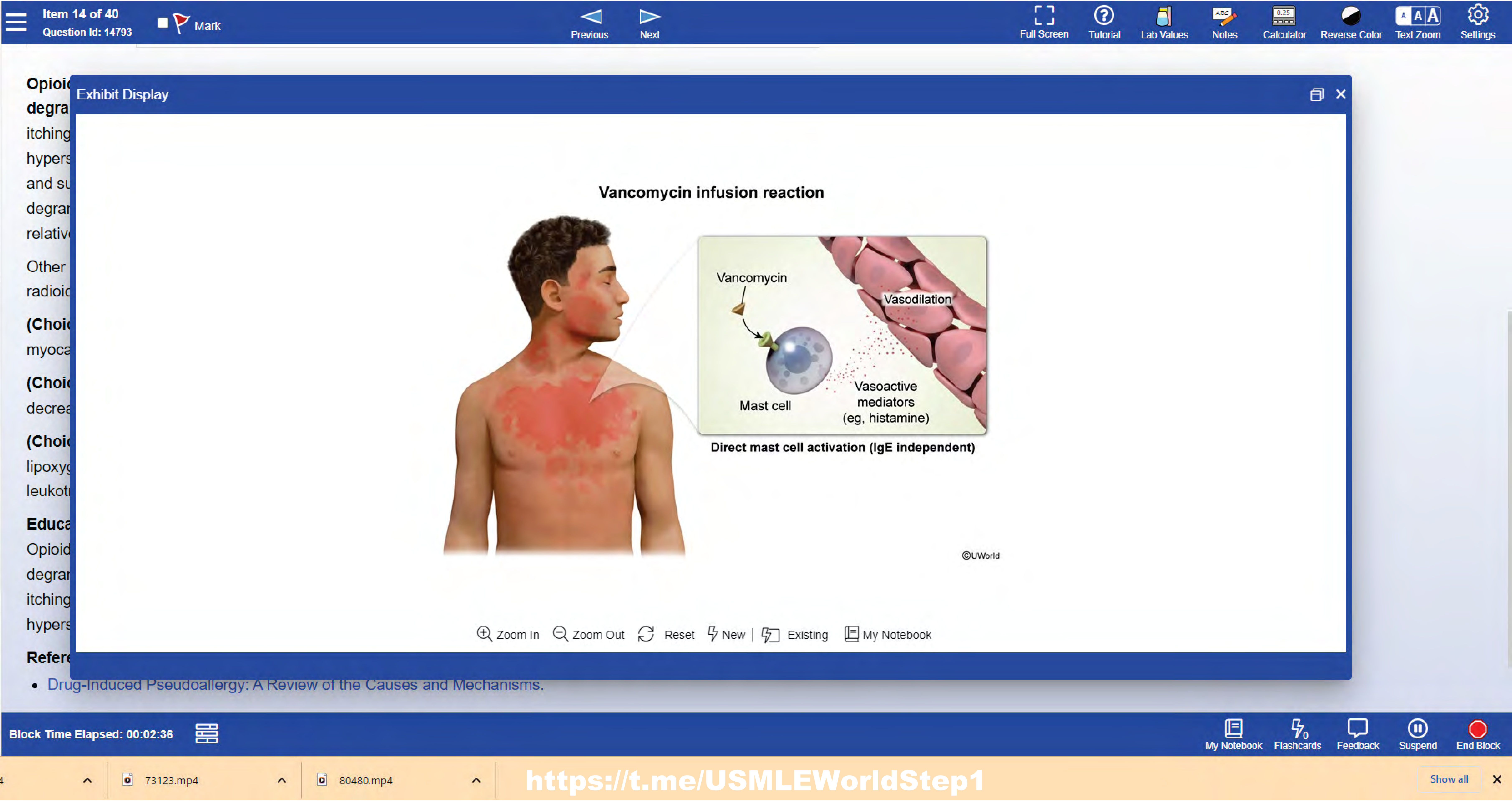
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- Drug-Induced Pseudoallergy: A Review of the Causes and Mechanisms.

Vancomycin infusion reaction

Vancomycin
Vasodilation
Mast cell
Vasoactive mediators (eg, histamine)

Direct mast cell activation (IgE independent)

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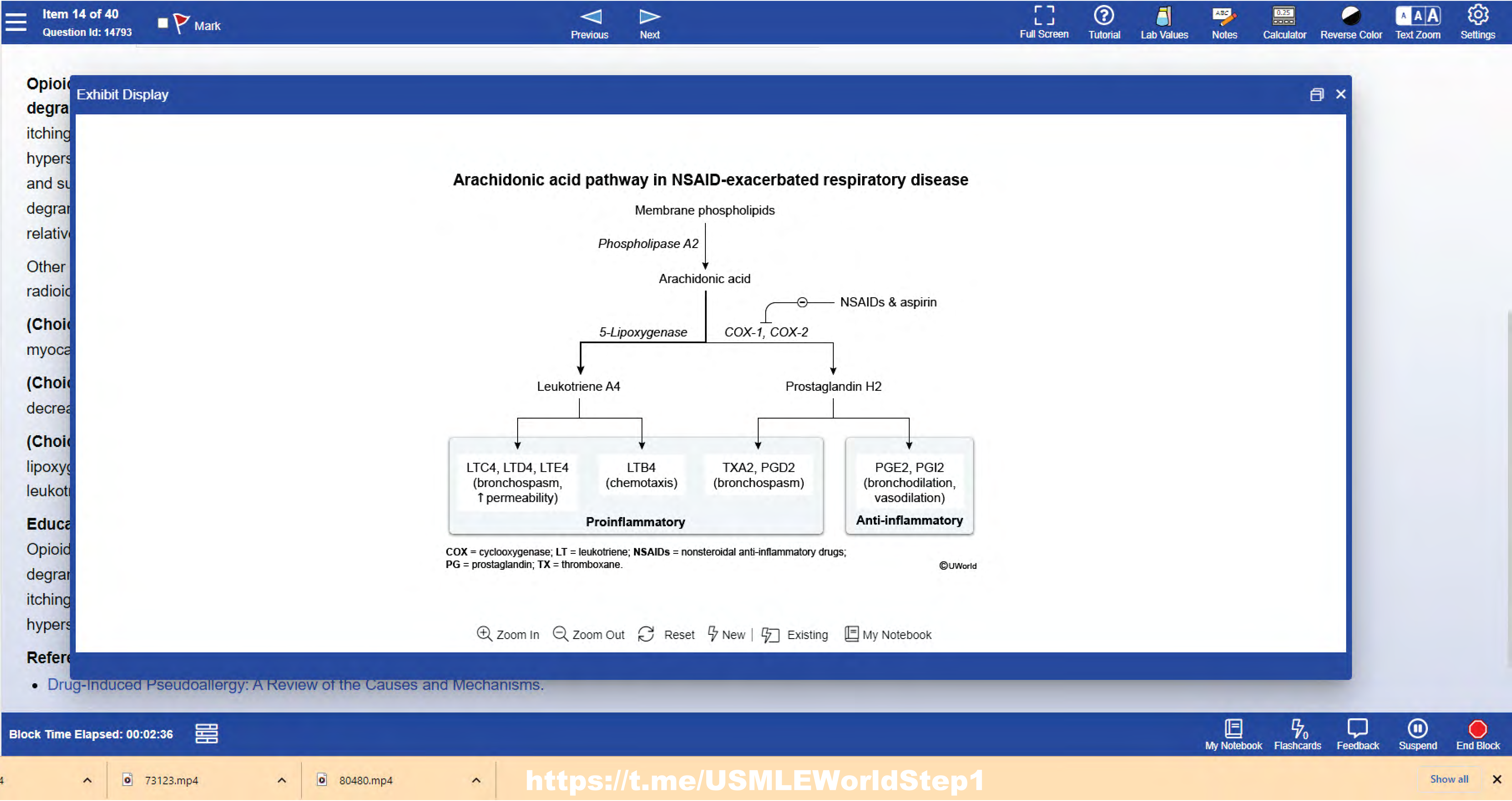
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- Drug-Induced Pseudoallergy: A Review of the Causes and Mechanisms.

Arachidonic acid pathway in NSAID-exacerbated respiratory disease

Membrane phospholipids
Phospholipase A2
Arachidonic acid
NSAIDs & aspirin
5-Lipoxygenase
COX-1, COX-2
Leukotriene A4
Prostaglandin H2
LTC4, LTD4, LTE4 (bronchospasm, ↑ permeability)
LTB4 (chemotaxis)
TXA2, PGD2 (bronchospasm)
PGE2, PGI2 (bronchodilation, vasodilation)
Proinflammatory
Anti-inflammatory

COX = cyclooxygenase; **LT** = leukotriene; **NSAIDs** = nonsteroidal anti-inflammatory drugs;
PG = prostaglandin; **TX** = thromboxane.

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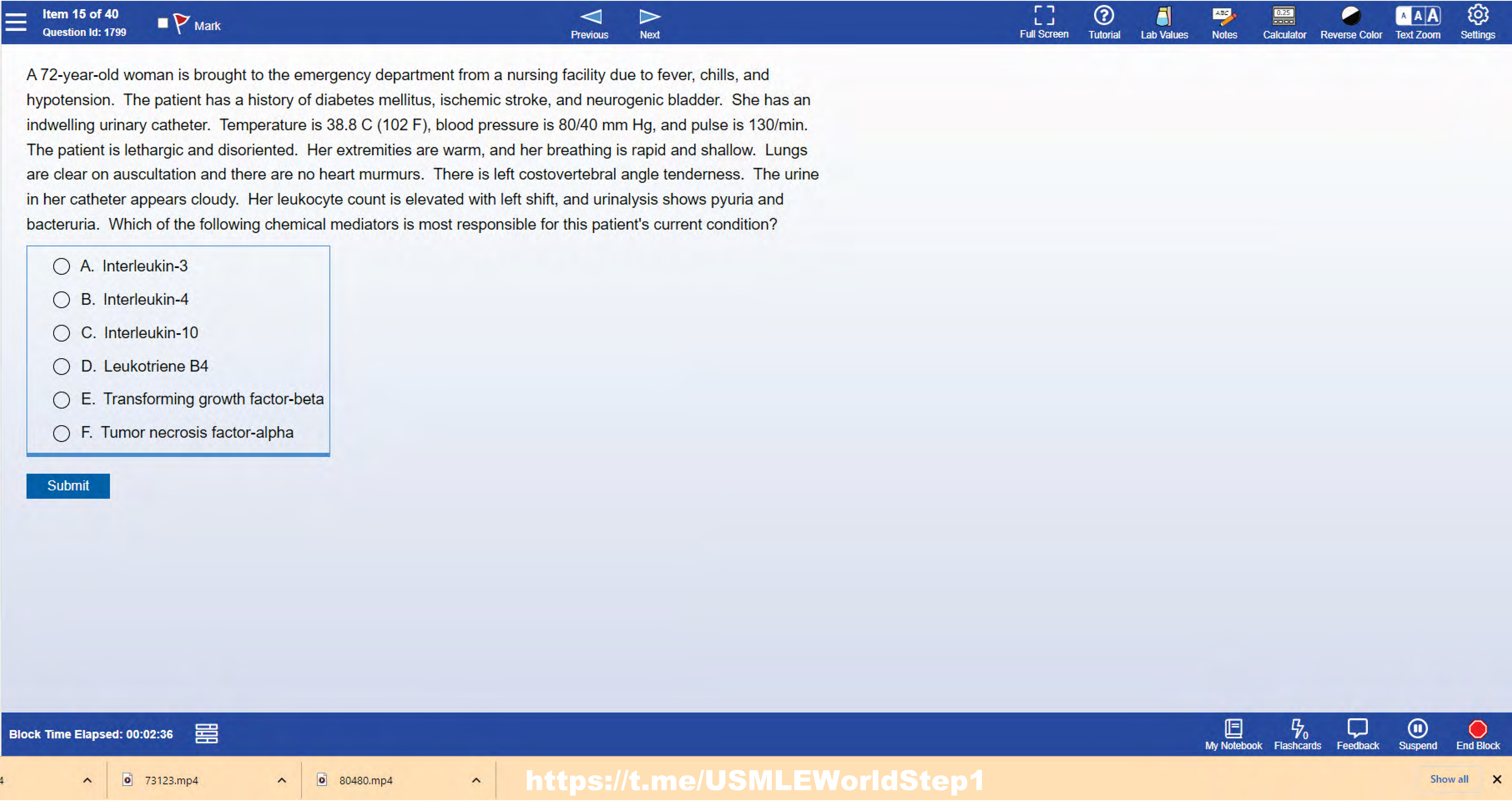
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A 72-year-old woman is brought to the emergency department from a nursing facility due to fever, chills, and hypotension. The patient has a history of diabetes mellitus, ischemic stroke, and neurogenic bladder. She has an indwelling urinary catheter. Temperature is 38.8 C (102 F), blood pressure is 80/40 mm Hg, and pulse is 130/min. The patient is lethargic and disoriented. Her extremities are warm, and her breathing is rapid and shallow. Lungs are clear on auscultation and there are no heart murmurs. There is left costovertebral angle tenderness. The urine in her catheter appears cloudy. Her leukocyte count is elevated with left shift, and urinalysis shows pyuria and bacteruria. Which of the following chemical mediators is most responsible for this patient's current condition?

- ○ A. Interleukin-3
- ○ B. Interleukin-4
- ○ C. Interleukin-10
- ○ D. Leukotriene B4
- ○ E. Transforming growth factor-beta
- ○ F. Tumor necrosis factor-alpha

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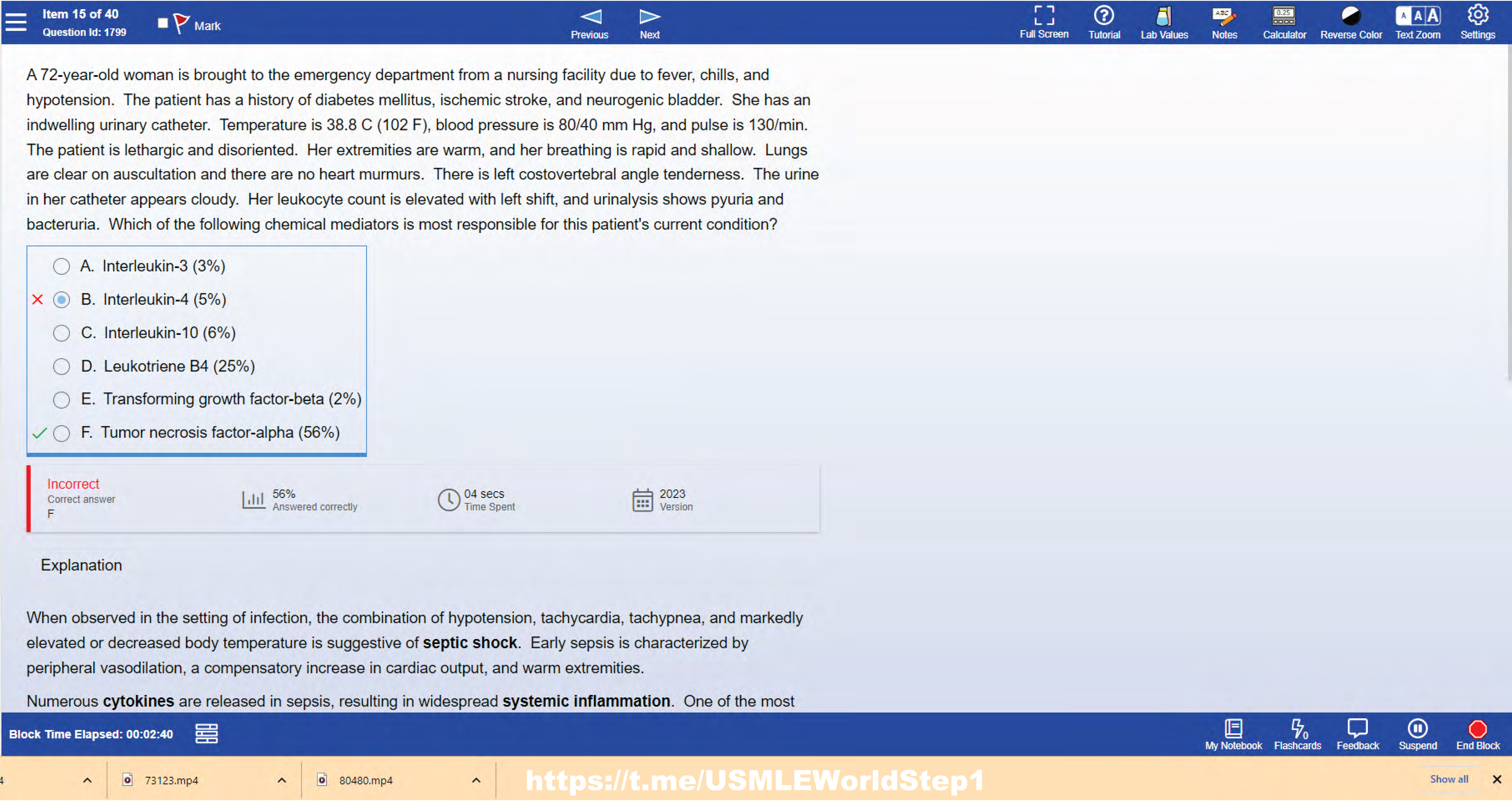
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○ A. Interleukin-3 (3%)

✗ ● B. Interleukin-4 (5%)

○ C. Interleukin-10 (6%)

○ D. Leukotriene B4 (25%)

○ E. Transforming growth factor-beta (2%)

✓ ○ F. Tumor necrosis factor-alpha (56%)

Incorrect
Correct answer
F

56%
Answered correctly

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Explanation

When observed in the setting of infection, the combination of hypotension, tachycardia, tachypnea, and markedly elevated or decreased body temperature is suggestive of **septic shock**. Early sepsis is characterized by peripheral vasodilation, a compensatory increase in cardiac output, and warm extremities.

Numerous **cytokines** are released in sepsis, resulting in widespread **systemic inflammation**. One of the most

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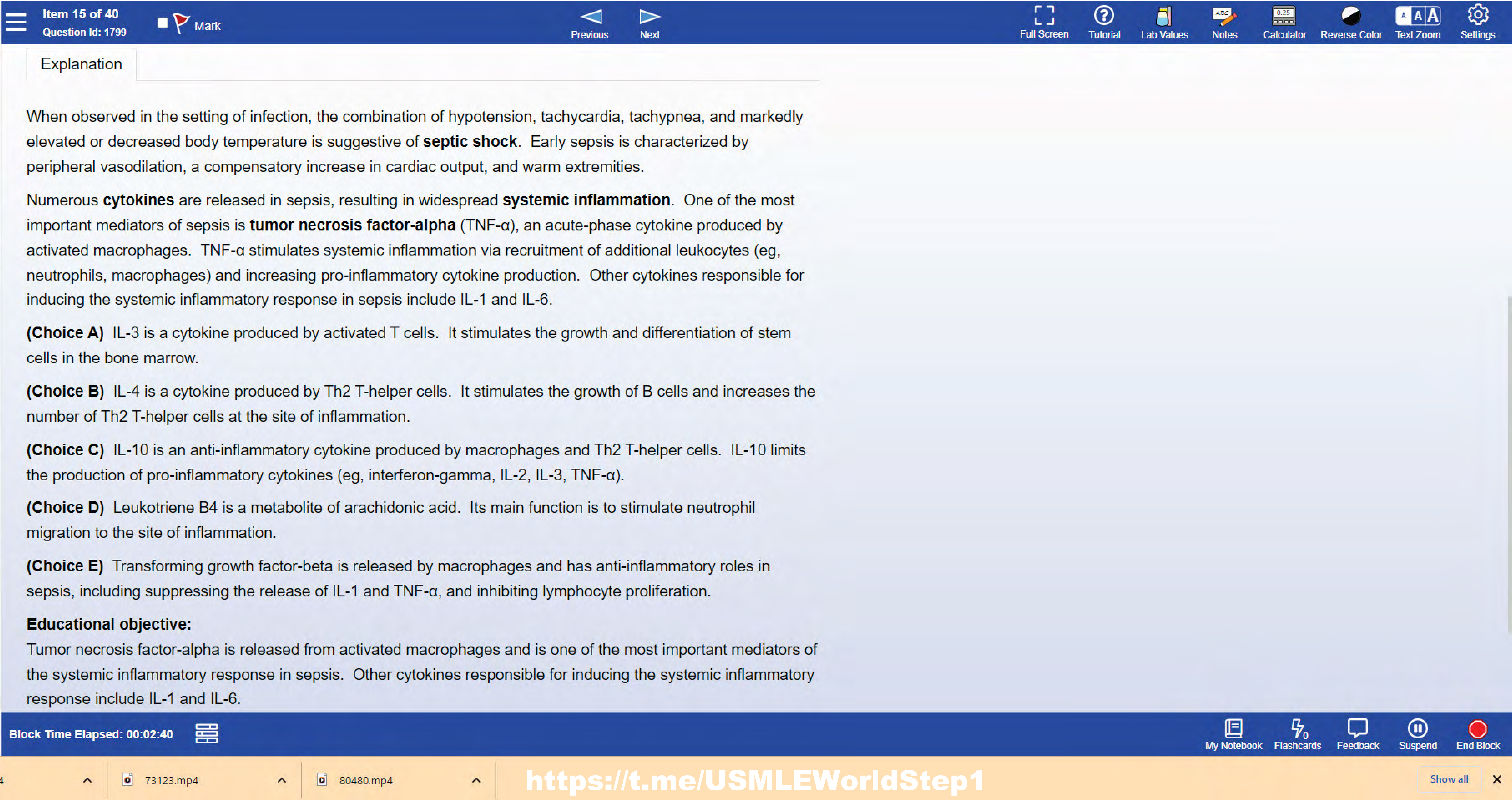
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When observed in the setting of infection, the combination of hypotension, tachycardia, tachypnea, and markedly elevated or decreased body temperature is suggestive of **septic shock**. Early sepsis is characterized by peripheral vasodilation, a compensatory increase in cardiac output, and warm extremities.

Numerous **cytokines** are released in sepsis, resulting in widespread **systemic inflammation**. One of the most important mediators of sepsis is **tumor necrosis factor-alpha** (TNF-α), an acute-phase cytokine produced by activated macrophages. TNF-α stimulates systemic inflammation via recruitment of additional leukocytes (eg, neutrophils, macrophages) and increasing pro-inflammatory cytokine production. Other cytokines responsible for inducing the systemic inflammatory response in sepsis include IL-1 and IL-6.

(Choice A) IL-3 is a cytokine produced by activated T cells. It stimulates the growth and differentiation of stem cells in the bone marrow.

(Choice B) IL-4 is a cytokine produced by Th2 T-helper cells. It stimulates the growth of B cells and increases the number of Th2 T-helper cells at the site of inflammation.

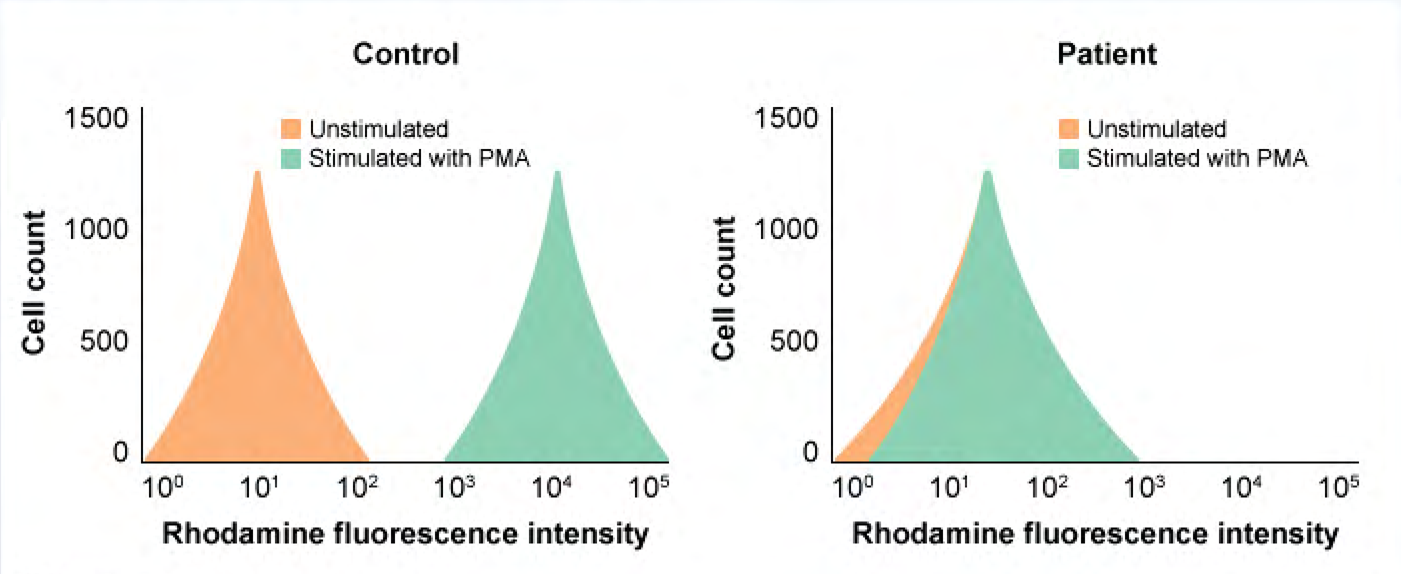
(Choice C) IL-10 is an anti-inflammatory cytokine produced by macrophages and Th2 T-helper cells. IL-10 limits the production of pro-inflammatory cytokines (eg, interferon-gamma, IL-2, IL-3, TNF-α).

(Choice D) Leukotriene B4 is a metabolite of arachidonic acid. Its main function is to stimulate neutrophil migration to the site of inflammation.

(Choice E) Transforming growth factor-beta is released by macrophages and has anti-inflammatory roles in sepsis, including suppressing the release of IL-1 and TNF-α, and inhibiting lymphocyte proliferation.

Educational objective:
Tumor necrosis factor-alpha is released from activated macrophages and is one of the most important mediators of the systemic inflammatory response in sepsis. Other cytokines responsible for inducing the systemic inflammatory response include IL-1 and IL-6.

A 15-month-old boy is brought to the emergency department due to fever and foot swelling. The patient first developed swelling of the right foot and fever 4 days ago. Today, swelling of the left foot also developed. Medical history is significant for a perianal abscess at 9 months of age. Imaging studies reveal osteomyelitis affecting the metatarsal bones of both feet. Intravenous antimicrobials are administered, but the patient still has fever and bilateral foot swelling 2 weeks later. Laboratory workup shows persistent neutrophilic leukocytosis. Bone biopsy culture grows *Staphylococcus aureus*. Evaluation for an underlying diagnosis is initiated; via use of a rhodamine derivative, the patient's peripheral blood is stimulated with phorbol myristate acetate (PMA) and compared with a control. Results of the test are shown in the image below:



PMA = phorbol myristate acetate. ©UWorld

Which of the following processes is most likely impaired in this patient?

○ A. Chemotaxis
○ B. Complement production
○ C. Opsonization
○ D. Phagocytic metabolism

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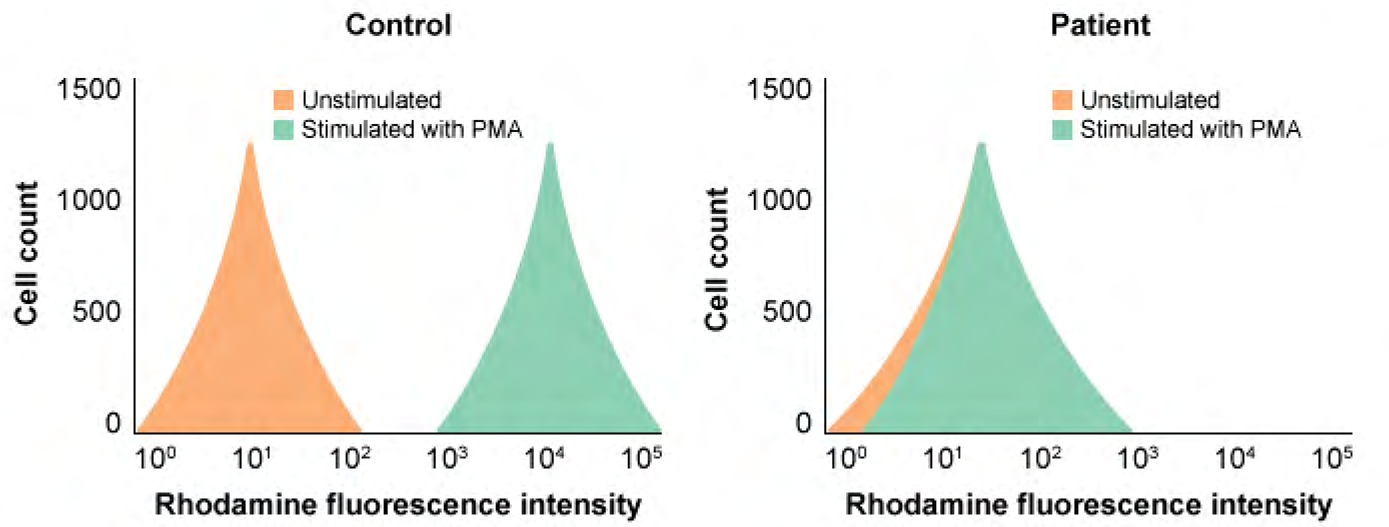

PMA = phorbol myristate acetate.

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○ D. Phagocytic metabolism

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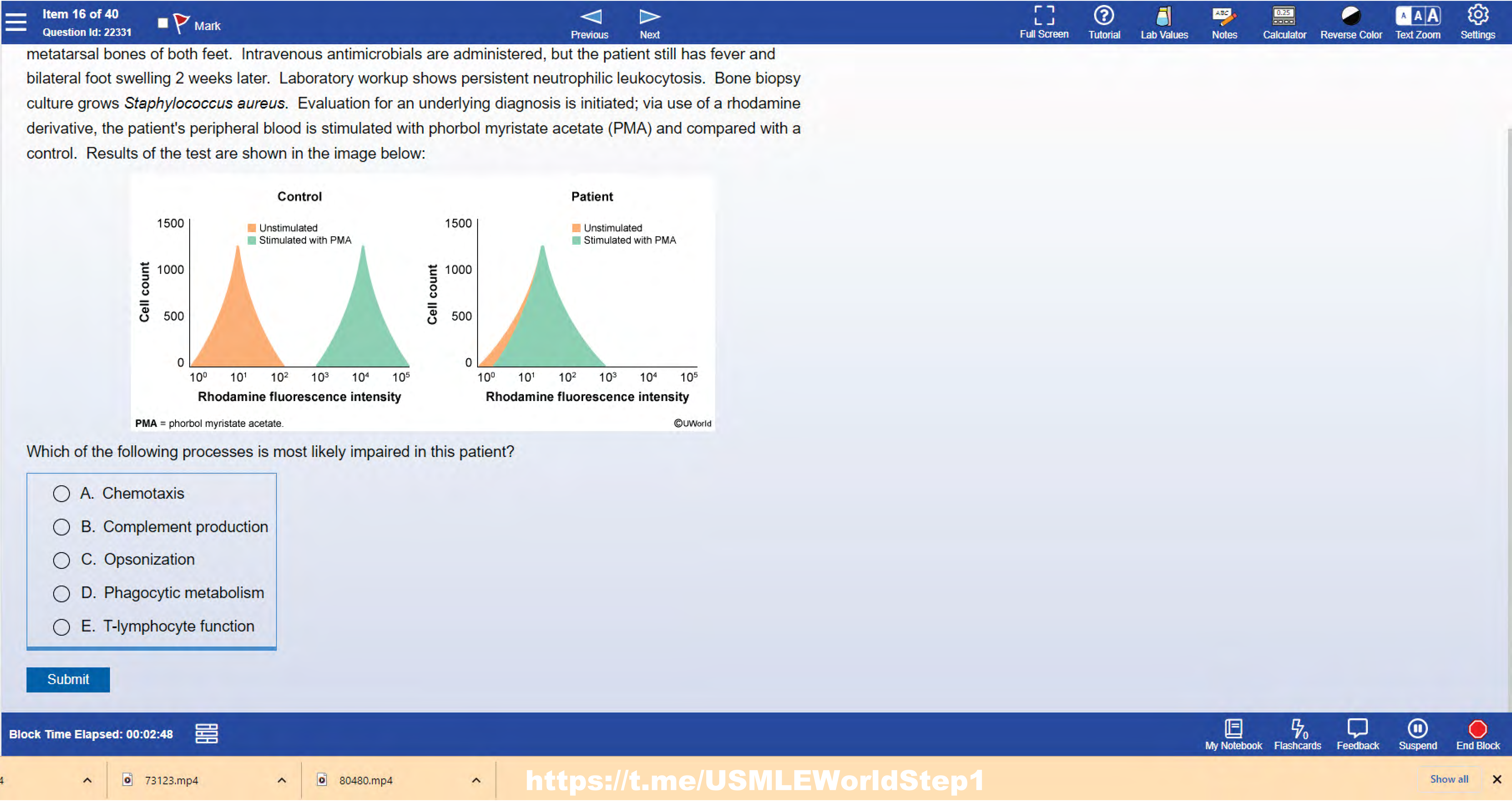
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metatarsal bones of both feet. Intravenous antimicrobials are administered, but the patient still has fever and bilateral foot swelling 2 weeks later. Laboratory workup shows persistent neutrophilic leukocytosis. Bone biopsy culture grows *Staphylococcus aureus*. Evaluation for an underlying diagnosis is initiated; via use of a rhodamine derivative, the patient's peripheral blood is stimulated with phorbol myristate acetate (PMA) and compared with a control. Results of the test are shown in the image below:

Control
Patient
Cell count
1500
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🟧 Unstimulated
🟩 Stimulated with PMA
10^0
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10^2
10^3
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10^5
Rhodamine fluorescence intensity

PMA = phorbol myristate acetate.

©UWorld

Which of the following processes is most likely impaired in this patient?

○ A. Chemotaxis
○ B. Complement production
○ C. Opsonization
○ D. Phagocytic metabolism
○ E. T-lymphocyte function

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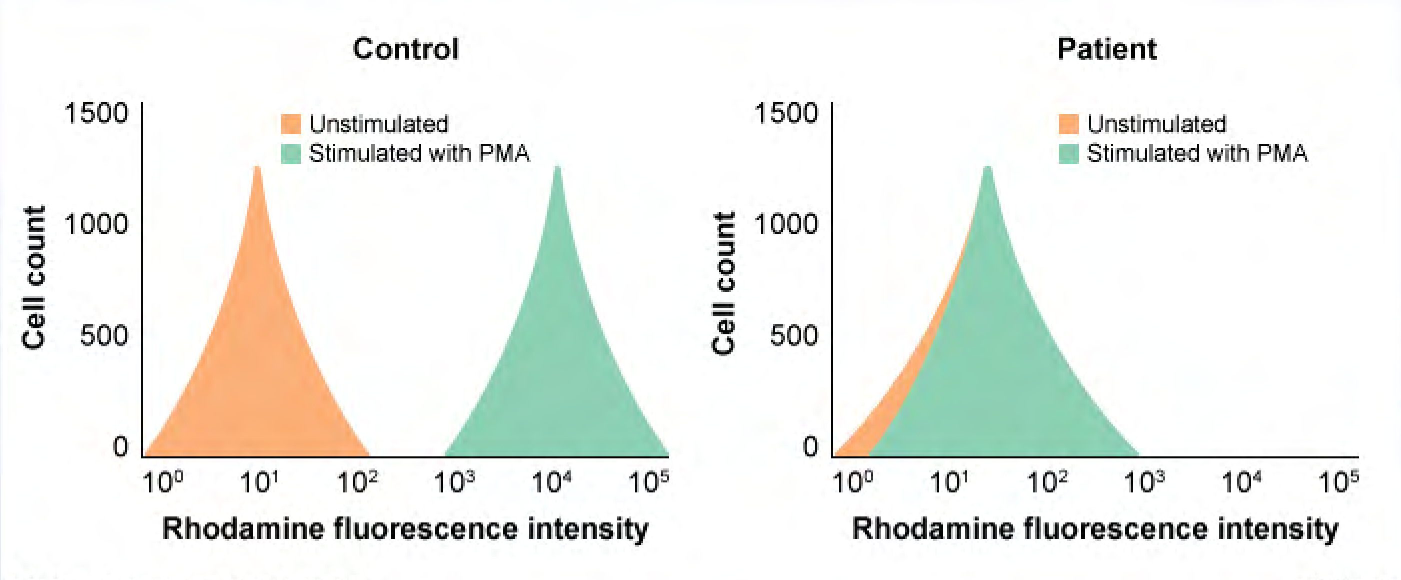
metatarsal bones of both feet. Intravenous antimicrobials are administered, but the patient still has fever and bilateral foot swelling 2 weeks later. Laboratory workup shows persistent neutrophilic leukocytosis. Bone biopsy culture grows *Staphylococcus aureus*. Evaluation for an underlying diagnosis is initiated; via use of a rhodamine derivative, the patient's peripheral blood is stimulated with phorbol myristate acetate (PMA) and compared with a control. Results of the test are shown in the image below:



PMA = phorbol myristate acetate.

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Which of the following processes is most likely impaired in this patient?

○ A. Chemotaxis (34%)

○ B. Complement production (6%)

✗ ● C. Opsonization (15%)

✓ ○ D. Phagocytic metabolism (36%)

○ E. T-lymphocyte function (7%)

Incorrect
Correct answer
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36%
Answered correctly

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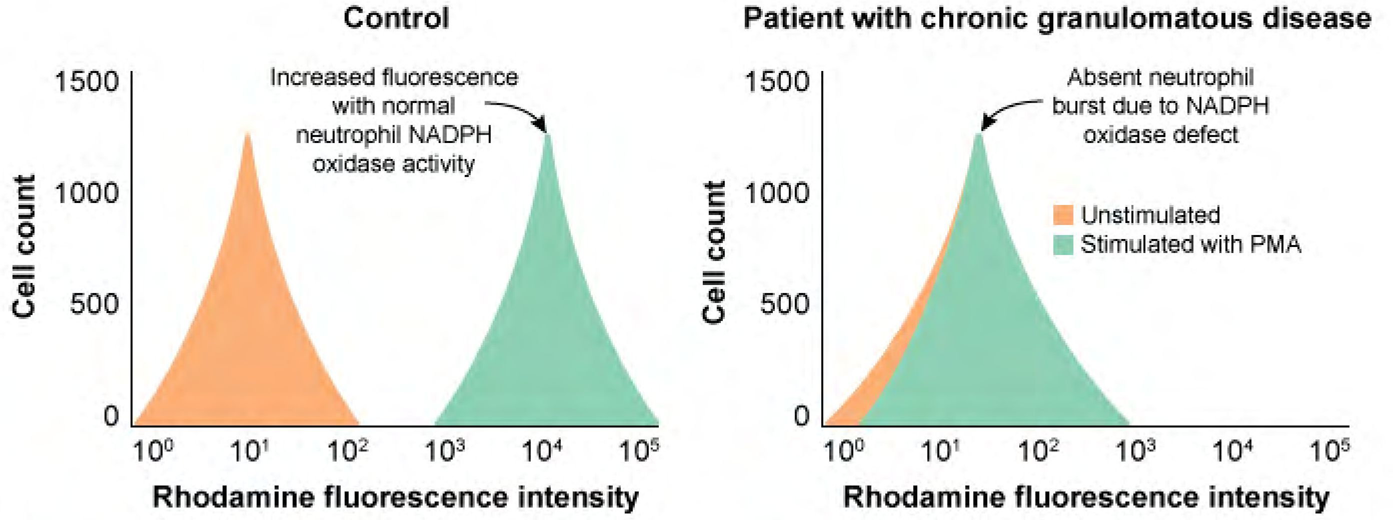

PMA = phorbol myristate acetate.

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(Choice B) Complement deficiencies often present with recurrent *Neisseria* infections, not *S aureus*

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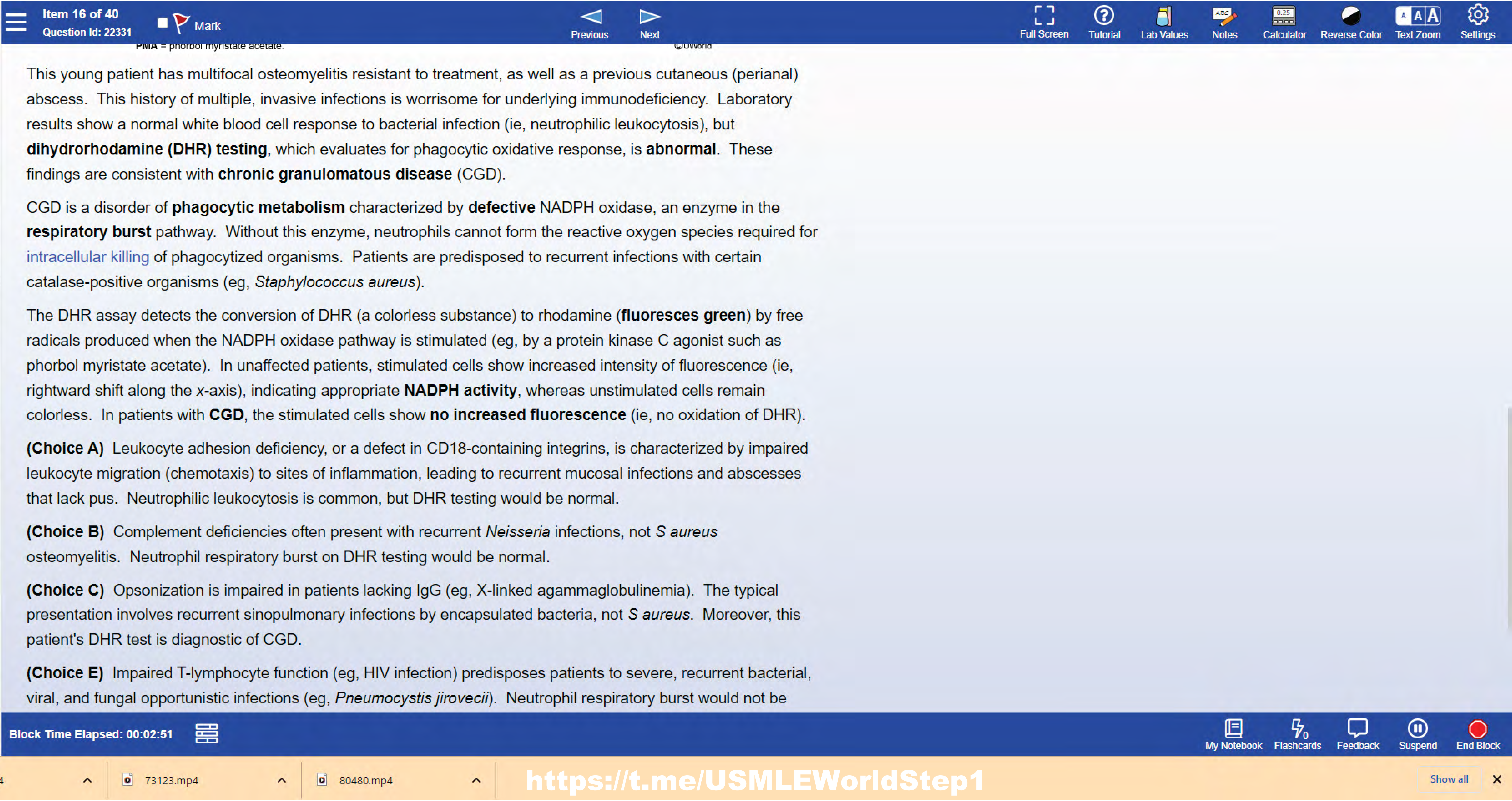

PMA = phorbol myristate acetate. ©UWorld

This young patient has multifocal osteomyelitis resistant to treatment, as well as a previous cutaneous (perianal) abscess. This history of multiple, invasive infections is worrisome for underlying immunodeficiency. Laboratory results show a normal white blood cell response to bacterial infection (ie, neutrophilic leukocytosis), but **dihydrorhodamine (DHR) testing**, which evaluates for phagocytic oxidative response, is **abnormal**. These findings are consistent with **chronic granulomatous disease** (CGD).

CGD is a disorder of **phagocytic metabolism** characterized by **defective** NADPH oxidase, an enzyme in the **respiratory burst** pathway. Without this enzyme, neutrophils cannot form the reactive oxygen species required for intracellular killing of phagocytized organisms. Patients are predisposed to recurrent infections with certain catalase-positive organisms (eg, *Staphylococcus aureus*).

The DHR assay detects the conversion of DHR (a colorless substance) to rhodamine (**fluoresces green**) by free radicals produced when the NADPH oxidase pathway is stimulated (eg, by a protein kinase C agonist such as phorbol myristate acetate). In unaffected patients, stimulated cells show increased intensity of fluorescence (ie, rightward shift along the *x*-axis), indicating appropriate **NADPH activity**, whereas unstimulated cells remain colorless. In patients with **CGD**, the stimulated cells show **no increased fluorescence** (ie, no oxidation of DHR).

(Choice A) Leukocyte adhesion deficiency, or a defect in CD18-containing integrins, is characterized by impaired leukocyte migration (chemotaxis) to sites of inflammation, leading to recurrent mucosal infections and abscesses that lack pus. Neutrophilic leukocytosis is common, but DHR testing would be normal.

(Choice B) Complement deficiencies often present with recurrent *Neisseria* infections, not *S aureus* osteomyelitis. Neutrophil respiratory burst on DHR testing would be normal.

(Choice C) Opsonization is impaired in patients lacking IgG (eg, X-linked agammaglobulinemia). The typical presentation involves recurrent sinopulmonary infections by encapsulated bacteria, not *S aureus*. Moreover, this patient's DHR test is diagnostic of CGD.

(Choice E) Impaired T-lymphocyte function (eg, HIV infection) predisposes patients to severe, recurrent bacterial, viral, and fungal opportunistic infections (eg, *Pneumocystis jirovecii*). Neutrophil respiratory burst would not be

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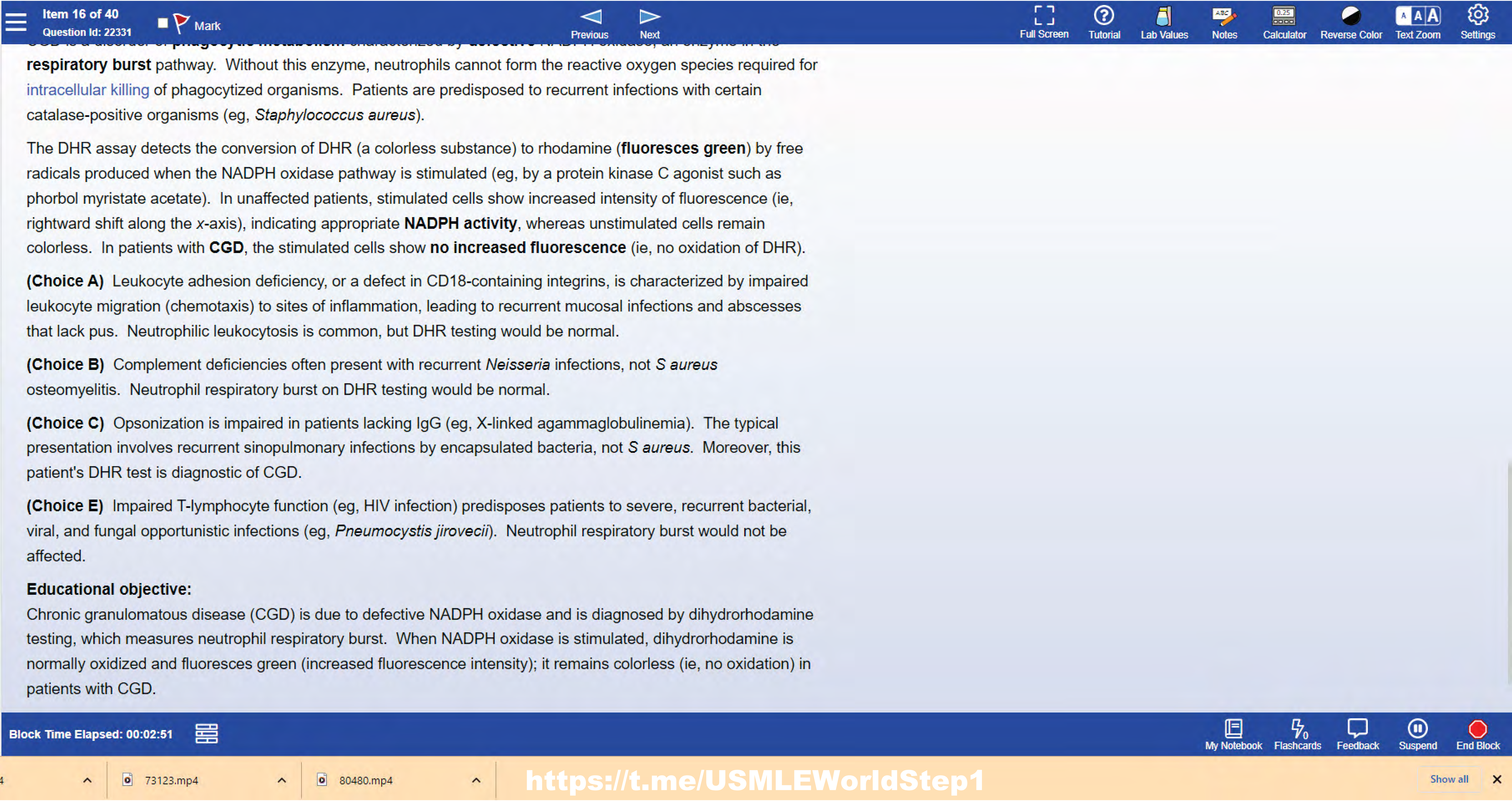

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(Choice E) Impaired T-lymphocyte function (eg, HIV infection) predisposes patients to severe, recurrent bacterial, viral, and fungal opportunistic infections (eg, *Pneumocystis jirovecii*). Neutrophil respiratory burst would not be affected.

Educational objective:

Chronic granulomatous disease (CGD) is due to defective NADPH oxidase and is diagnosed by dihydrorhodamine testing, which measures neutrophil respiratory burst. When NADPH oxidase is stimulated, dihydrorhodamine is normally oxidized and fluoresces green (increased fluorescence intensity); it remains colorless (ie, no oxidation) in patients with CGD.

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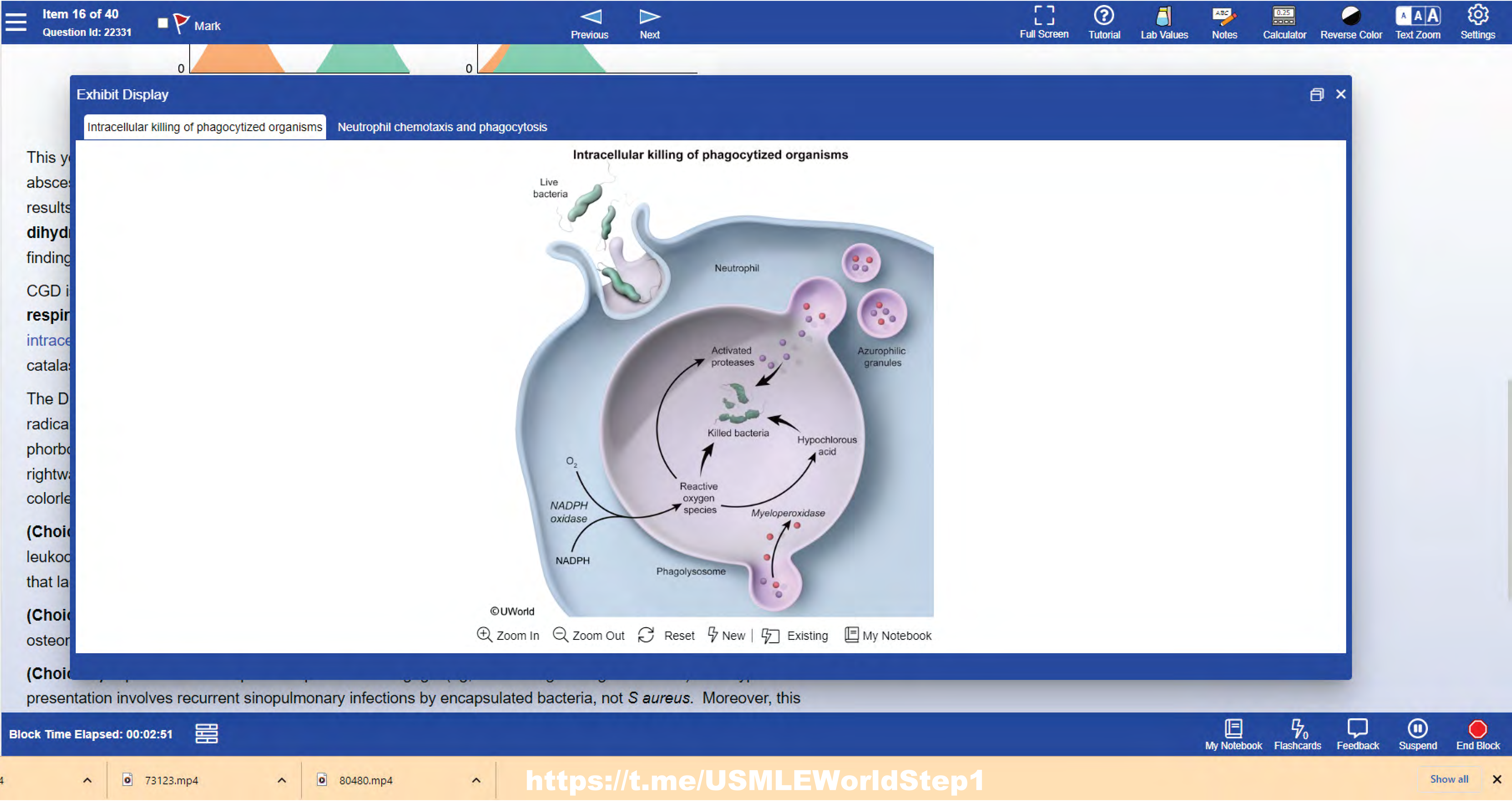
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Azurophilic granules
Activated proteases
Killed bacteria
Hypochlorous acid
O_2
Reactive oxygen species
NADPH oxidase
Myeloperoxidase
NADPH
Phagolysosome
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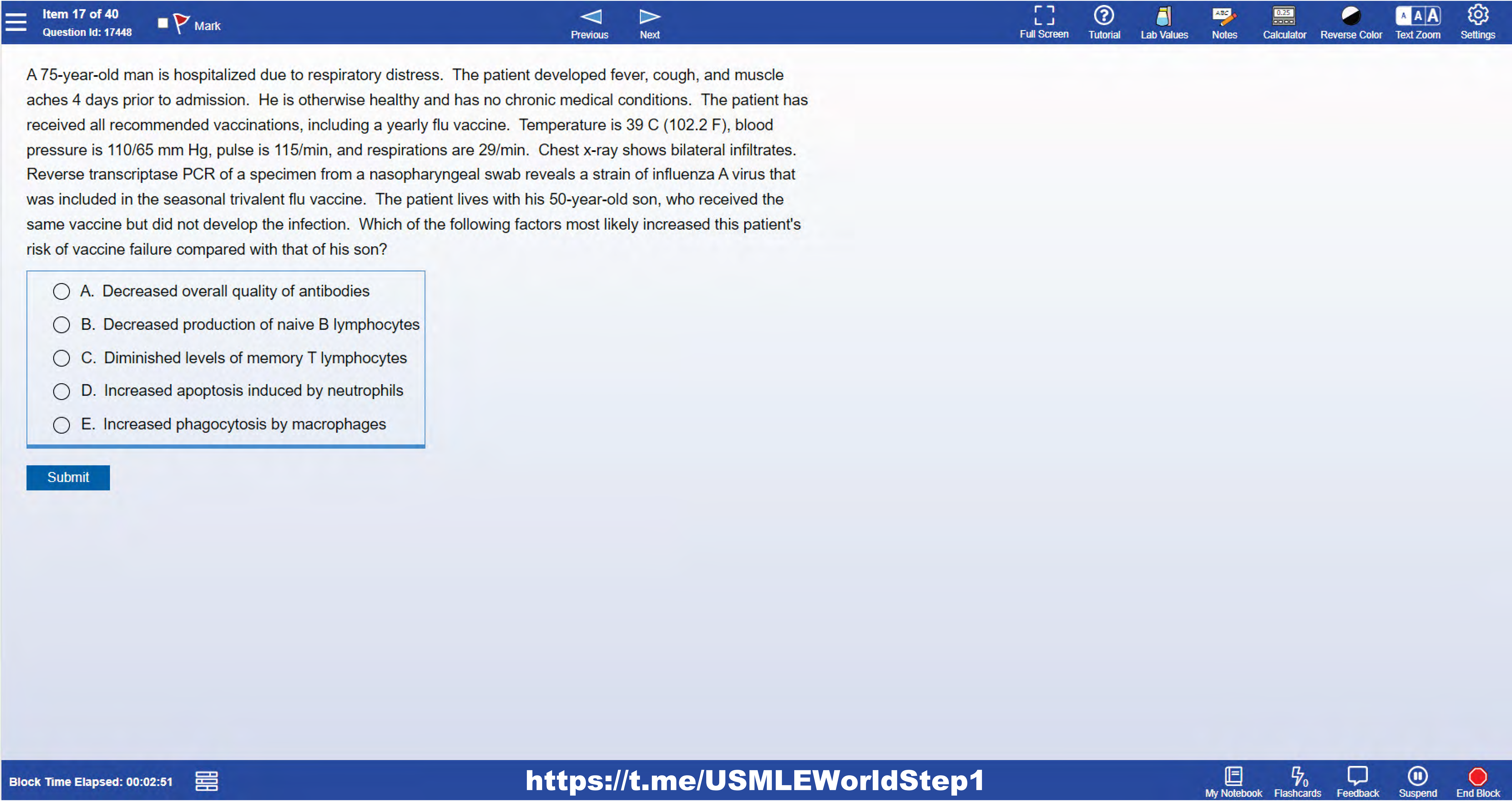
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A 75-year-old man is hospitalized due to respiratory distress. The patient developed fever, cough, and muscle aches 4 days prior to admission. He is otherwise healthy and has no chronic medical conditions. The patient has received all recommended vaccinations, including a yearly flu vaccine. Temperature is 39 C (102.2 F), blood pressure is 110/65 mm Hg, pulse is 115/min, and respirations are 29/min. Chest x-ray shows bilateral infiltrates. Reverse transcriptase PCR of a specimen from a nasopharyngeal swab reveals a strain of influenza A virus that was included in the seasonal trivalent flu vaccine. The patient lives with his 50-year-old son, who received the same vaccine but did not develop the infection. Which of the following factors most likely increased this patient's risk of vaccine failure compared with that of his son?

○ A. Decreased overall quality of antibodies
○ B. Decreased production of naive B lymphocytes
○ C. Diminished levels of memory T lymphocytes
○ D. Increased apoptosis induced by neutrophils
○ E. Increased phagocytosis by macrophages

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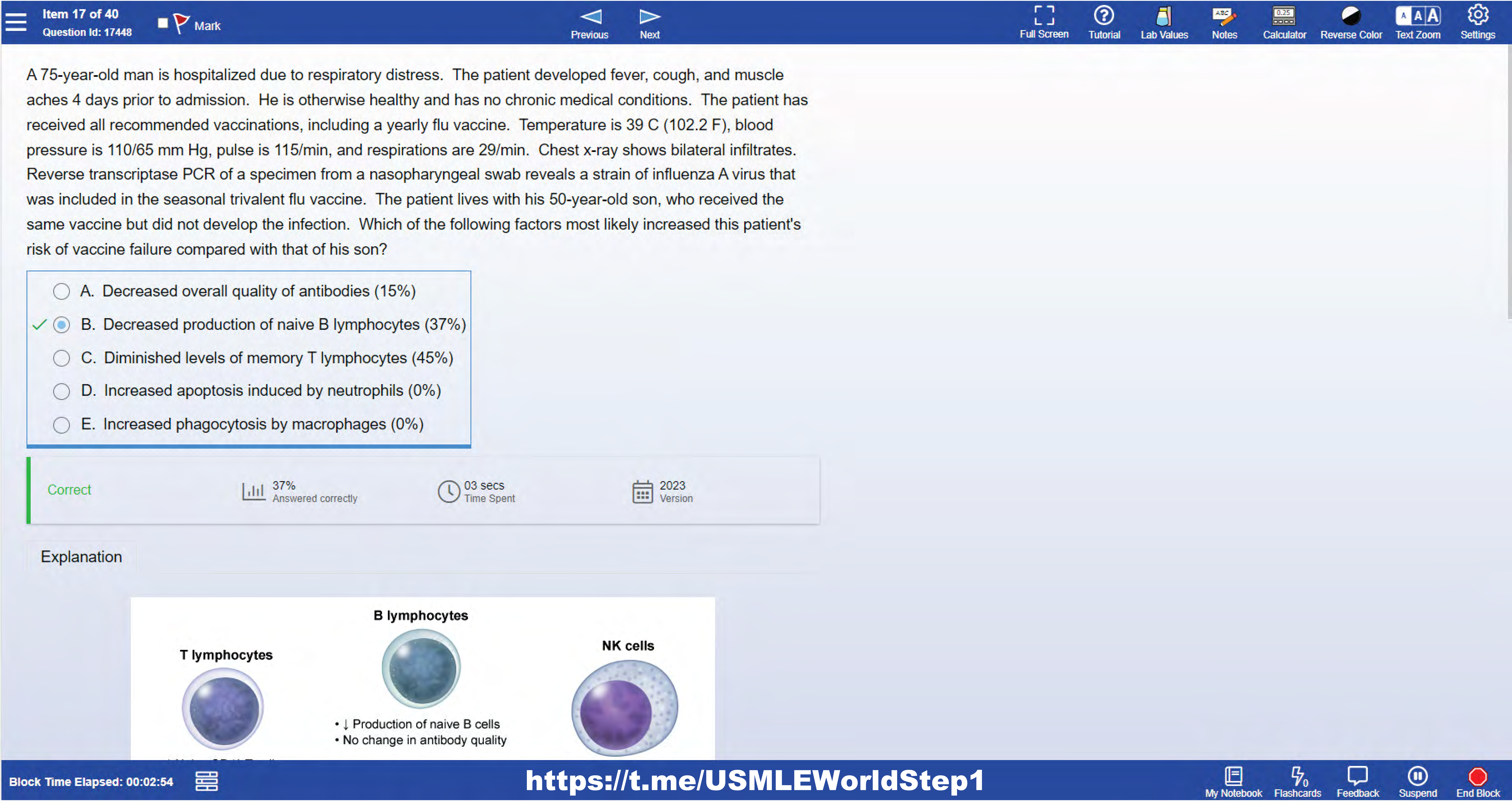
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- ○ A. Decreased overall quality of antibodies (15%)
- ✓ ● B. Decreased production of naive B lymphocytes (37%)
- ○ C. Diminished levels of memory T lymphocytes (45%)
- ○ D. Increased apoptosis induced by neutrophils (0%)
- ○ E. Increased phagocytosis by macrophages (0%)

Correct
37% Answered correctly
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Explanation

T lymphocytes
B lymphocytes
NK cells

- ↓ Production of naive B cells
- No change in antibody quality

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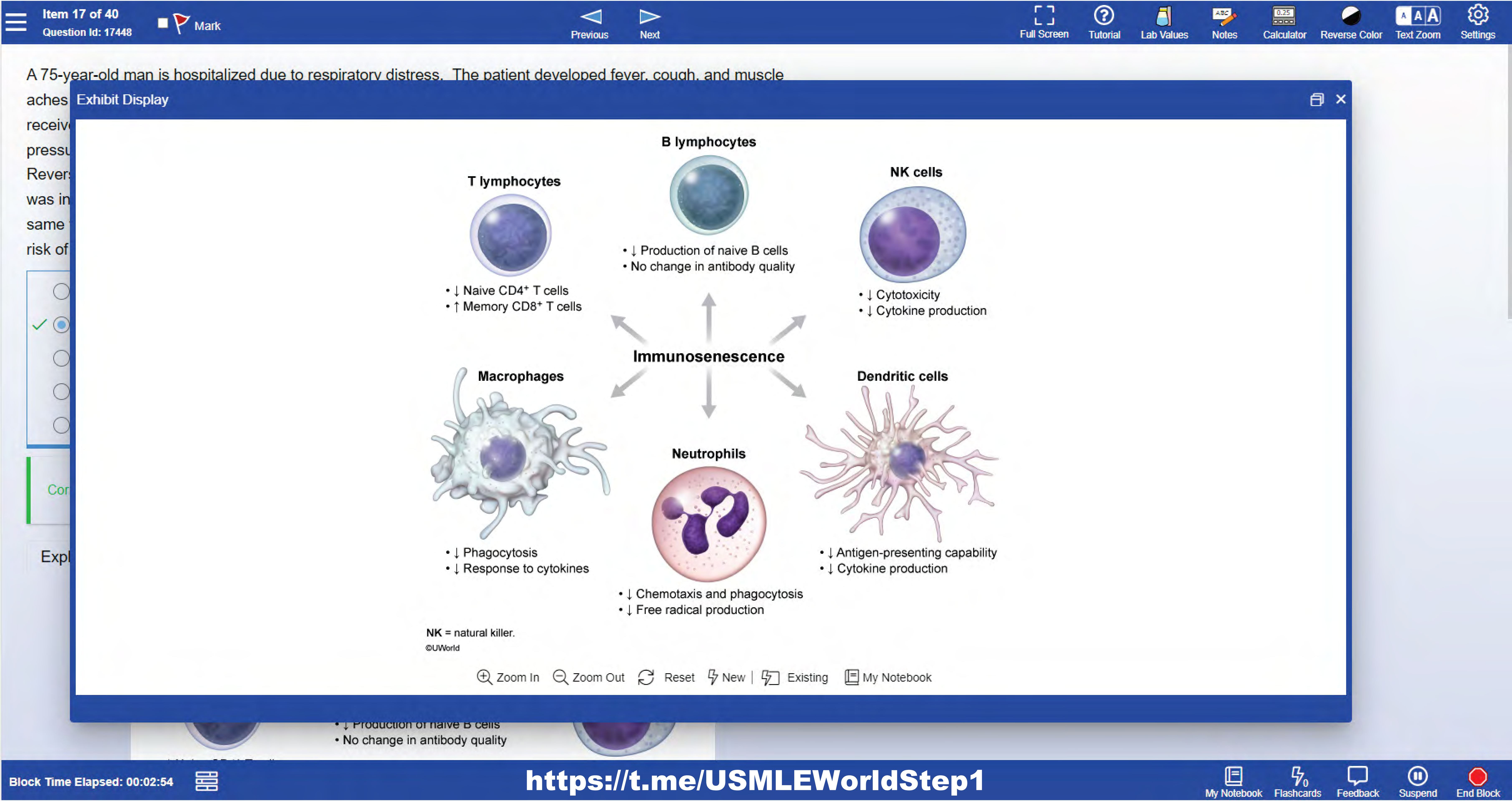
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A 75-year-old man is hospitalized due to respiratory distress. The patient developed fever, cough, and muscle

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B lymphocytes
T lymphocytes
NK cells
Immunosenescence
Macrophages
Neutrophils
Dendritic cells

B lymphocytes
- ↓ Production of naive B cells
- No change in antibody quality

T lymphocytes
- ↓ Naive CD4⁺ T cells
- ↑ Memory CD8⁺ T cells

NK cells
- ↓ Cytotoxicity
- ↓ Cytokine production

Macrophages
- ↓ Phagocytosis
- ↓ Response to cytokines

Neutrophils
- ↓ Chemotaxis and phagocytosis
- ↓ Free radical production

Dendritic cells
- ↓ Antigen-presenting capability
- ↓ Cytokine production

NK = natural killer.

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• ↓ Production of naive B cells
• No change in antibody quality

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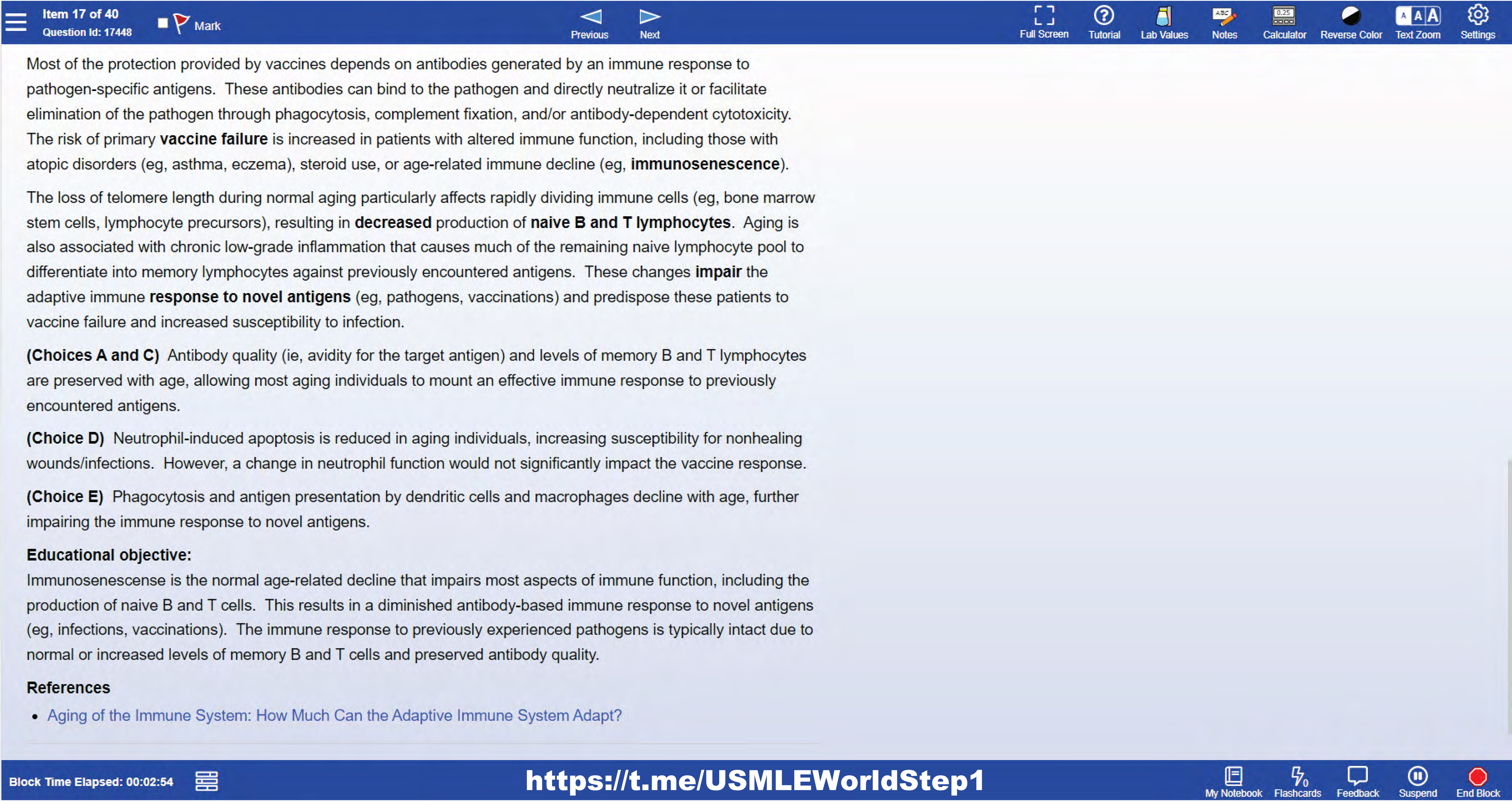


Most of the protection provided by vaccines depends on antibodies generated by an immune response to pathogen-specific antigens. These antibodies can bind to the pathogen and directly neutralize it or facilitate elimination of the pathogen through phagocytosis, complement fixation, and/or antibody-dependent cytotoxicity. The risk of primary **vaccine failure** is increased in patients with altered immune function, including those with atopic disorders (eg, asthma, eczema), steroid use, or age-related immune decline (eg, **immunosenescence**).

The loss of telomere length during normal aging particularly affects rapidly dividing immune cells (eg, bone marrow stem cells, lymphocyte precursors), resulting in **decreased** production of **naive B and T lymphocytes**. Aging is also associated with chronic low-grade inflammation that causes much of the remaining naive lymphocyte pool to differentiate into memory lymphocytes against previously encountered antigens. These changes **impair** the adaptive immune **response to novel antigens** (eg, pathogens, vaccinations) and predispose these patients to vaccine failure and increased susceptibility to infection.

(Choices A and C) Antibody quality (ie, avidity for the target antigen) and levels of memory B and T lymphocytes are preserved with age, allowing most aging individuals to mount an effective immune response to previously encountered antigens.

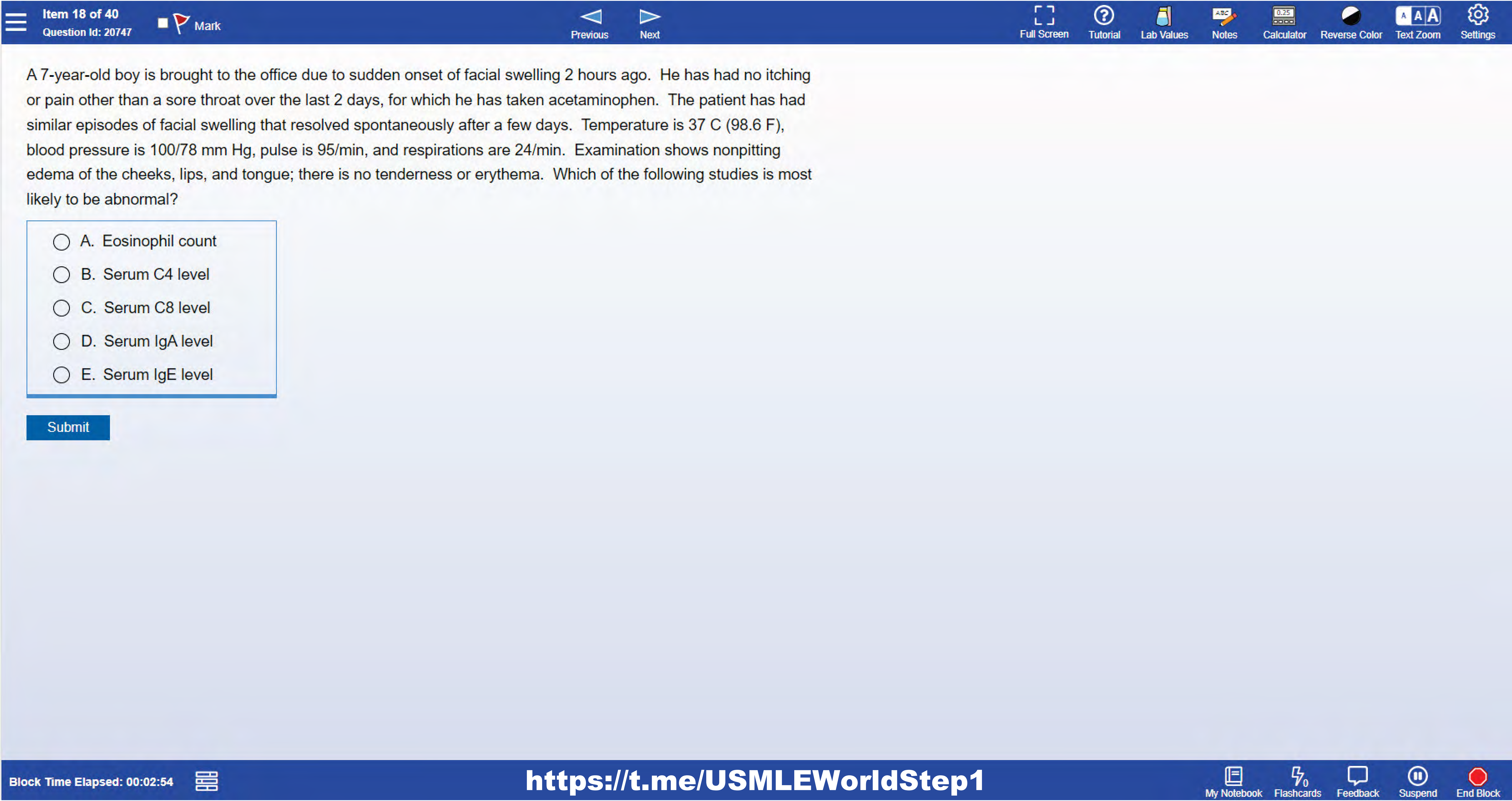
(Choice D) Neutrophil-induced apoptosis is reduced in aging individuals, increasing susceptibility for nonhealing wounds/infections. However, a change in neutrophil function would not significantly impact the vaccine response.

(Choice E) Phagocytosis and antigen presentation by dendritic cells and macrophages decline with age, further impairing the immune response to novel antigens.

Educational objective:
Immunosenescense is the normal age-related decline that impairs most aspects of immune function, including the production of naive B and T cells. This results in a diminished antibody-based immune response to novel antigens (eg, infections, vaccinations). The immune response to previously experienced pathogens is typically intact due to normal or increased levels of memory B and T cells and preserved antibody quality.

References

- Aging of the Immune System: How Much Can the Adaptive Immune System Adapt?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A 7-year-old boy is brought to the office due to sudden onset of facial swelling 2 hours ago. He has had no itching or pain other than a sore throat over the last 2 days, for which he has taken acetaminophen. The patient has had similar episodes of facial swelling that resolved spontaneously after a few days. Temperature is 37 C (98.6 F), blood pressure is 100/78 mm Hg, pulse is 95/min, and respirations are 24/min. Examination shows nonpitting edema of the cheeks, lips, and tongue; there is no tenderness or erythema. Which of the following studies is most likely to be abnormal?

○ A. Eosinophil count
○ B. Serum C4 level
○ C. Serum C8 level
○ D. Serum IgA level
○ E. Serum IgE level

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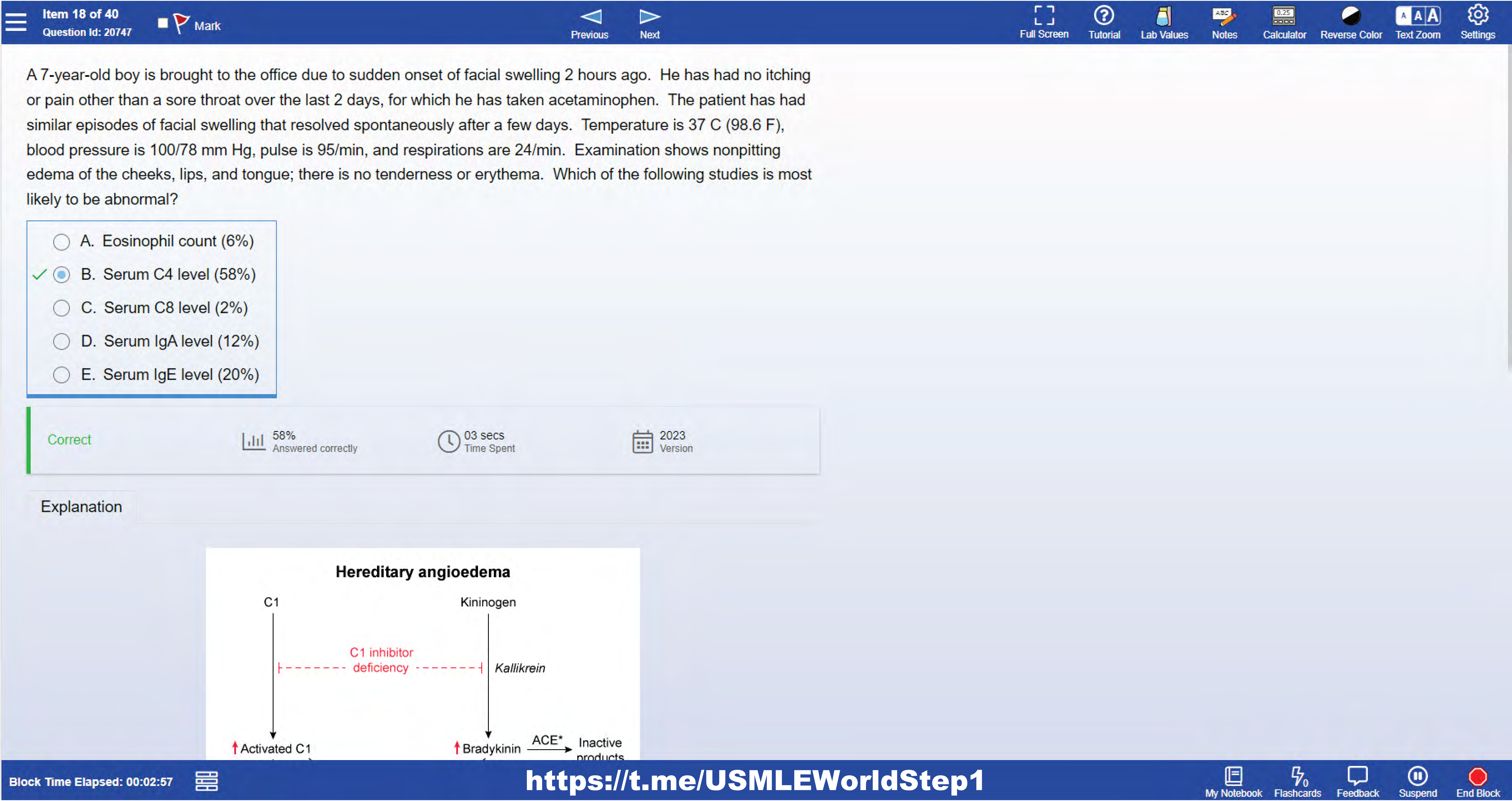
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○ A. Eosinophil count (6%)

✓ ● B. Serum C4 level (58%)

○ C. Serum C8 level (2%)

○ D. Serum IgA level (12%)

○ E. Serum IgE level (20%)

Correct

58% Answered correctly

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2023 Version

Explanation

Hereditary angioedema

C1
Kininogen
C1 inhibitor deficiency
Kallikrein
↑Activated C1
↑Bradykinin
ACE*
Inactive products
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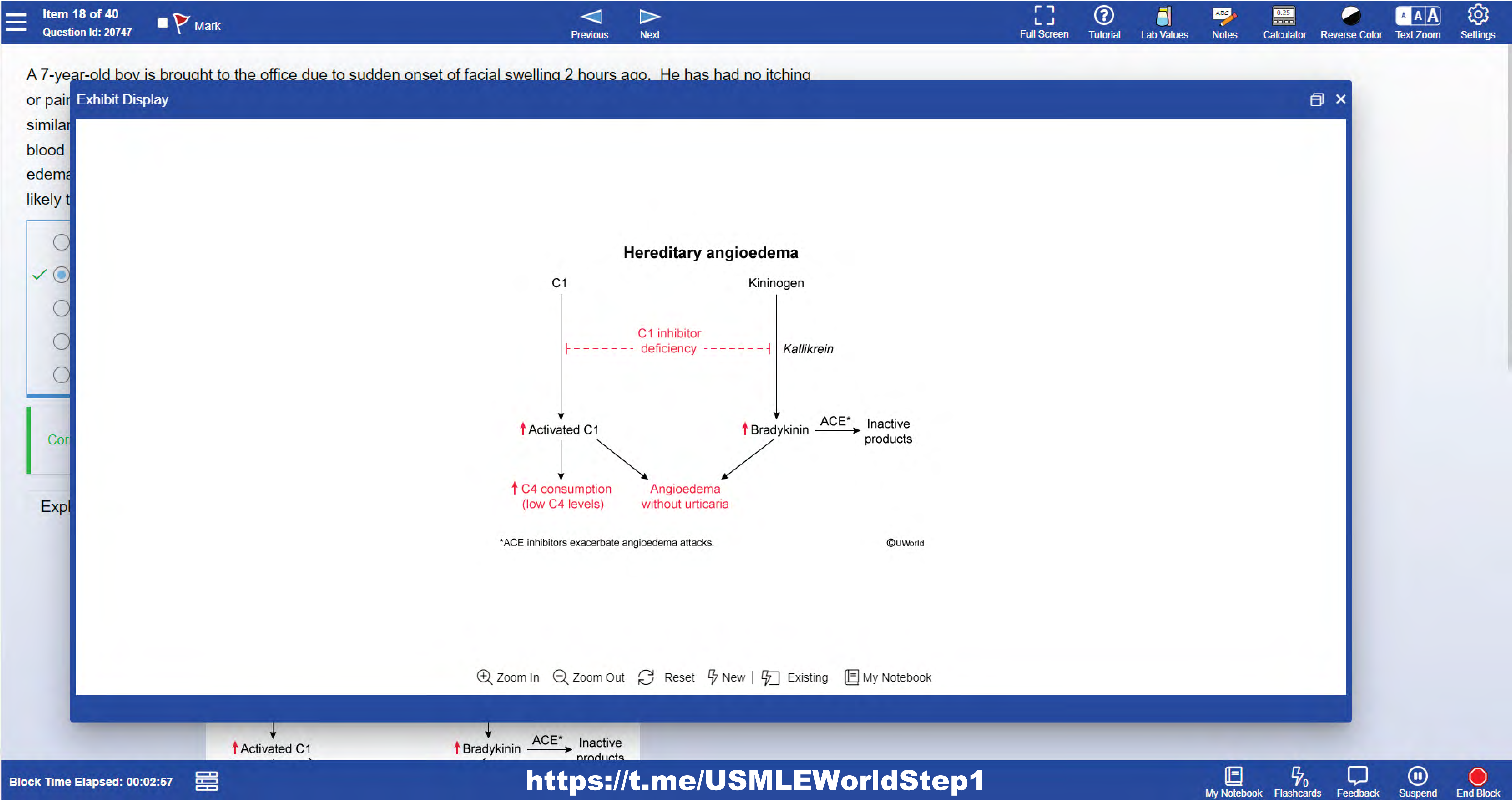
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Hereditary angioedema

C1
Kininogen
C1 inhibitor
deficiency
Kallikrein
↑ Activated C1
↑ Bradykinin
ACE*
Inactive
products
↑ C4 consumption
(low C4 levels)
Angioedema
without urticaria

*ACE inhibitors exacerbate angioedema attacks.

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↑ Activated C1
↑ Bradykinin ACE* Inactive
products

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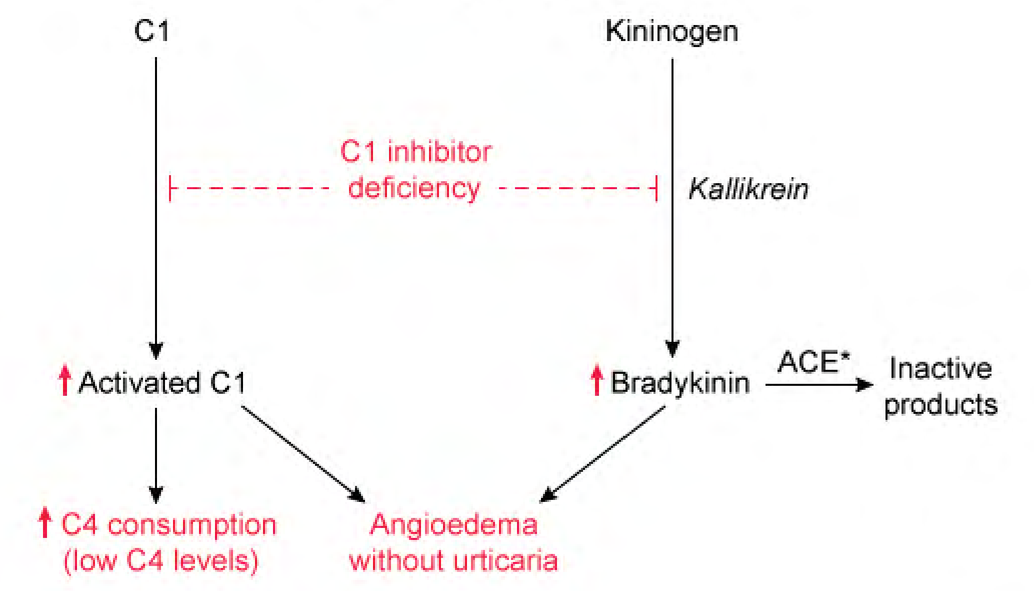
C1 inhibitor

Exhibit Display

Hereditary angioedema


C1
Kininogen
C1 inhibitor deficiency
Kallikrein
↑ Activated C1
↑ Bradykinin
ACE*
Inactive products
↑ C4 consumption (low C4 levels)
Angioedema without urticaria

*ACE inhibitors exacerbate angioedema attacks.

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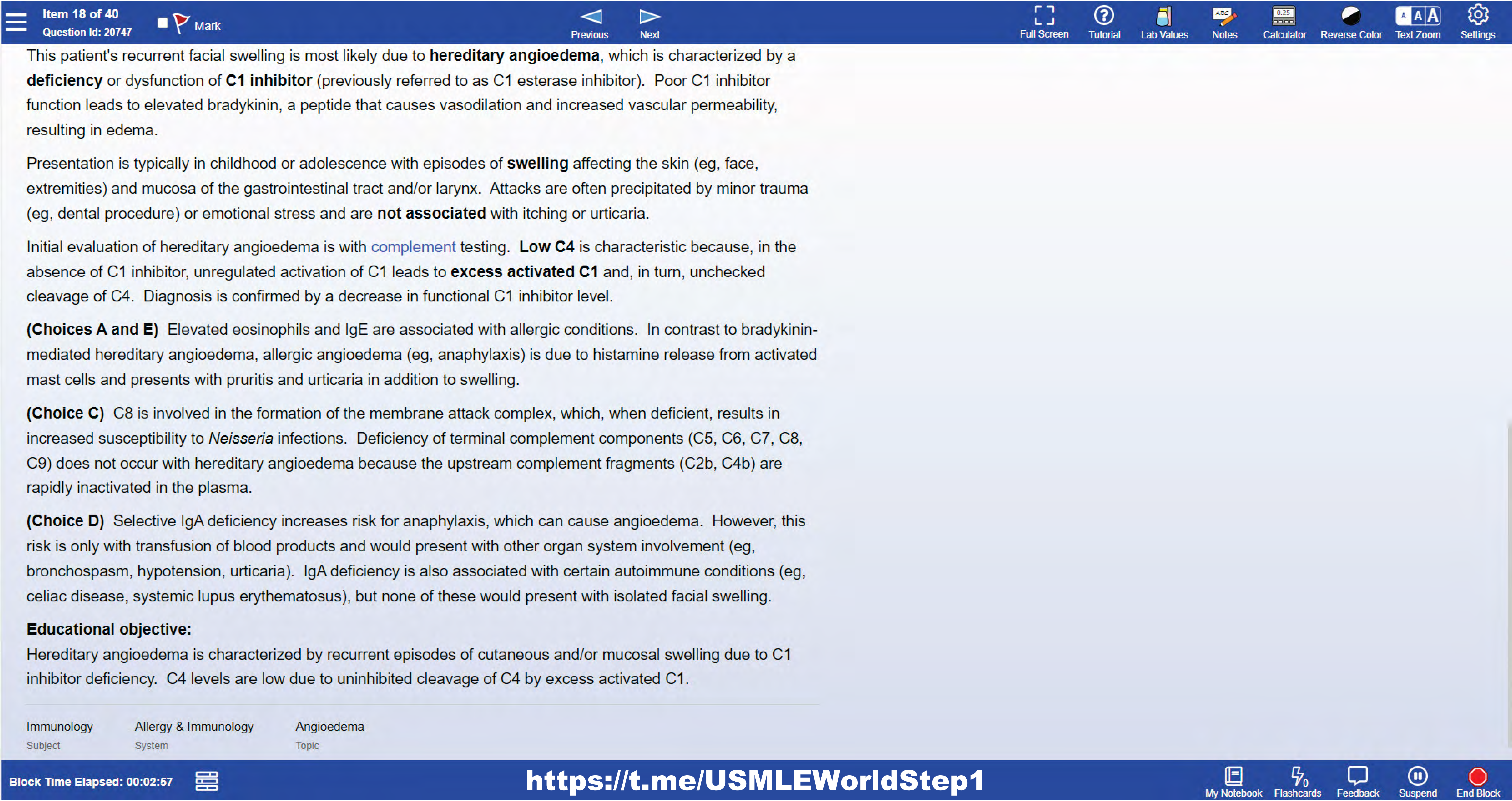

This patient's recurrent facial swelling is most likely due to **hereditary angioedema**, which is characterized by a **deficiency** or dysfunction of **C1 inhibitor** (previously referred to as C1 esterase inhibitor). Poor C1 inhibitor function leads to elevated bradykinin, a peptide that causes vasodilation and increased vascular permeability, resulting in edema.

Presentation is typically in childhood or adolescence with episodes of **swelling** affecting the skin (eg, face, extremities) and mucosa of the gastrointestinal tract and/or larynx. Attacks are often precipitated by minor trauma (eg, dental procedure) or emotional stress and are **not associated** with itching or urticaria.

Initial evaluation of hereditary angioedema is with complement testing. **Low C4** is characteristic because, in the absence of C1 inhibitor, unregulated activation of C1 leads to **excess activated C1** and, in turn, unchecked cleavage of C4. Diagnosis is confirmed by a decrease in functional C1 inhibitor level.

(Choices A and E) Elevated eosinophils and IgE are associated with allergic conditions. In contrast to bradykinin-mediated hereditary angioedema, allergic angioedema (eg, anaphylaxis) is due to histamine release from activated mast cells and presents with pruritis and urticaria in addition to swelling.

(Choice C) C8 is involved in the formation of the membrane attack complex, which, when deficient, results in increased susceptibility to *Neisseria* infections. Deficiency of terminal complement components (C5, C6, C7, C8, C9) does not occur with hereditary angioedema because the upstream complement fragments (C2b, C4b) are rapidly inactivated in the plasma.

(Choice D) Selective IgA deficiency increases risk for anaphylaxis, which can cause angioedema. However, this risk is only with transfusion of blood products and would present with other organ system involvement (eg, bronchospasm, hypotension, urticaria). IgA deficiency is also associated with certain autoimmune conditions (eg, celiac disease, systemic lupus erythematosus), but none of these would present with isolated facial swelling.

Educational objective:

Hereditary angioedema is characterized by recurrent episodes of cutaneous and/or mucosal swelling due to C1 inhibitor deficiency. C4 levels are low due to uninhibited cleavage of C4 by excess activated C1.

Immunology	Allergy & Immunology	Angioedema
Subject	System	Topic

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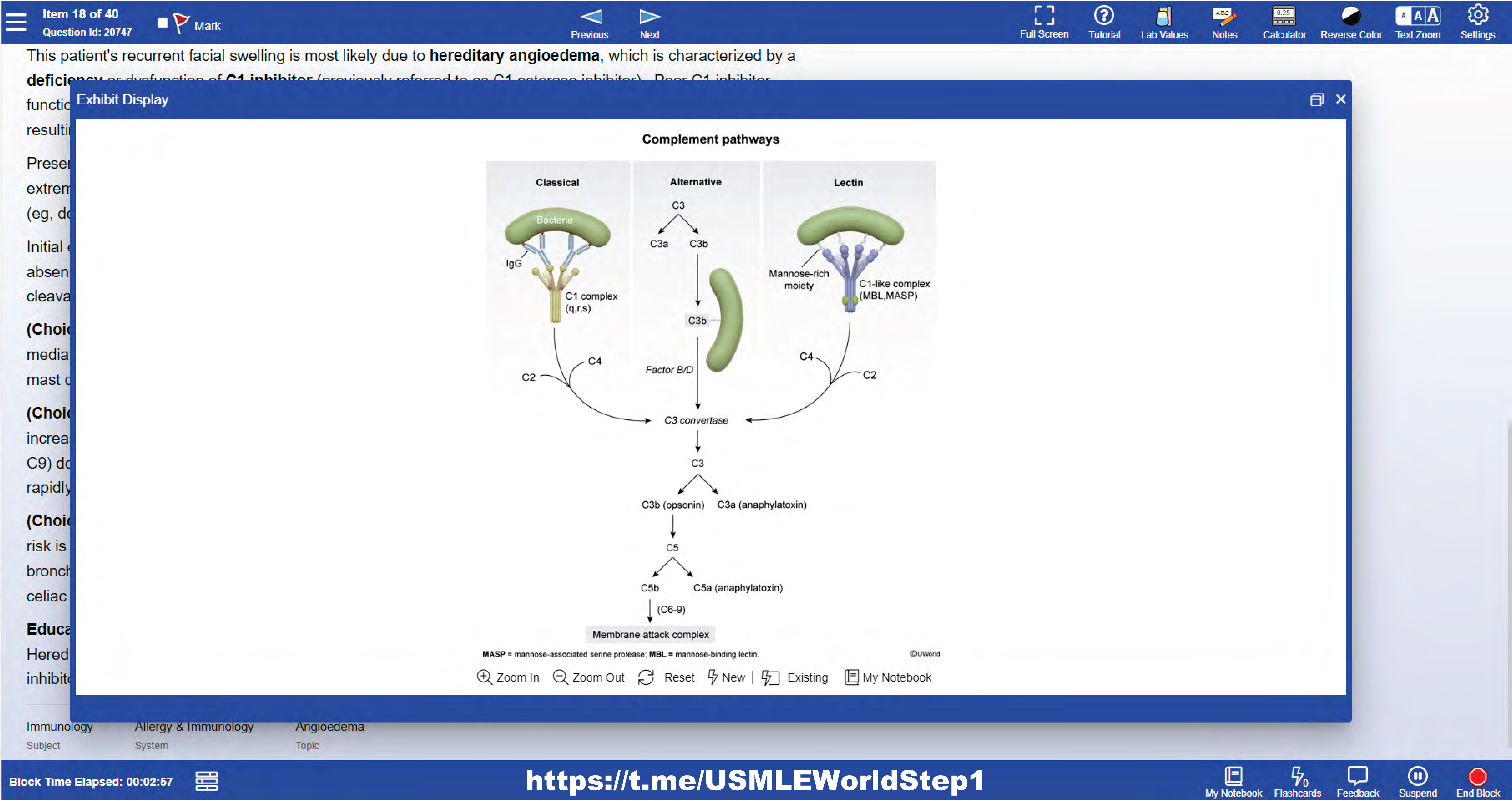
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This patient's recurrent facial swelling is most likely due to **hereditary angioedema**, which is characterized by a **deficiency or dysfunction of C1 inhibitor** (previously referred to as C1 esterase inhibitor). Poor C1 inhibitor

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Complement pathways

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Bacteria
IgG
C1 complex (q,r,s)
C2
C4
Alternative
C3
C3a
C3b
C3b
Factor B/D
Lectin
Mannose-rich moiety
C1-like complex (MBL,MASP)
C4
C2
C3 convertase
C3
C3b (opsonin)
C3a (anaphylatoxin)
C5
C5b
C5a (anaphylatoxin)
(C6-9)
Membrane attack complex

MASP = mannose-associated serine protease; **MBL** = mannose-binding lectin.

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Immunology	Allergy & Immunology	Angioedema
Subject	System	Topic

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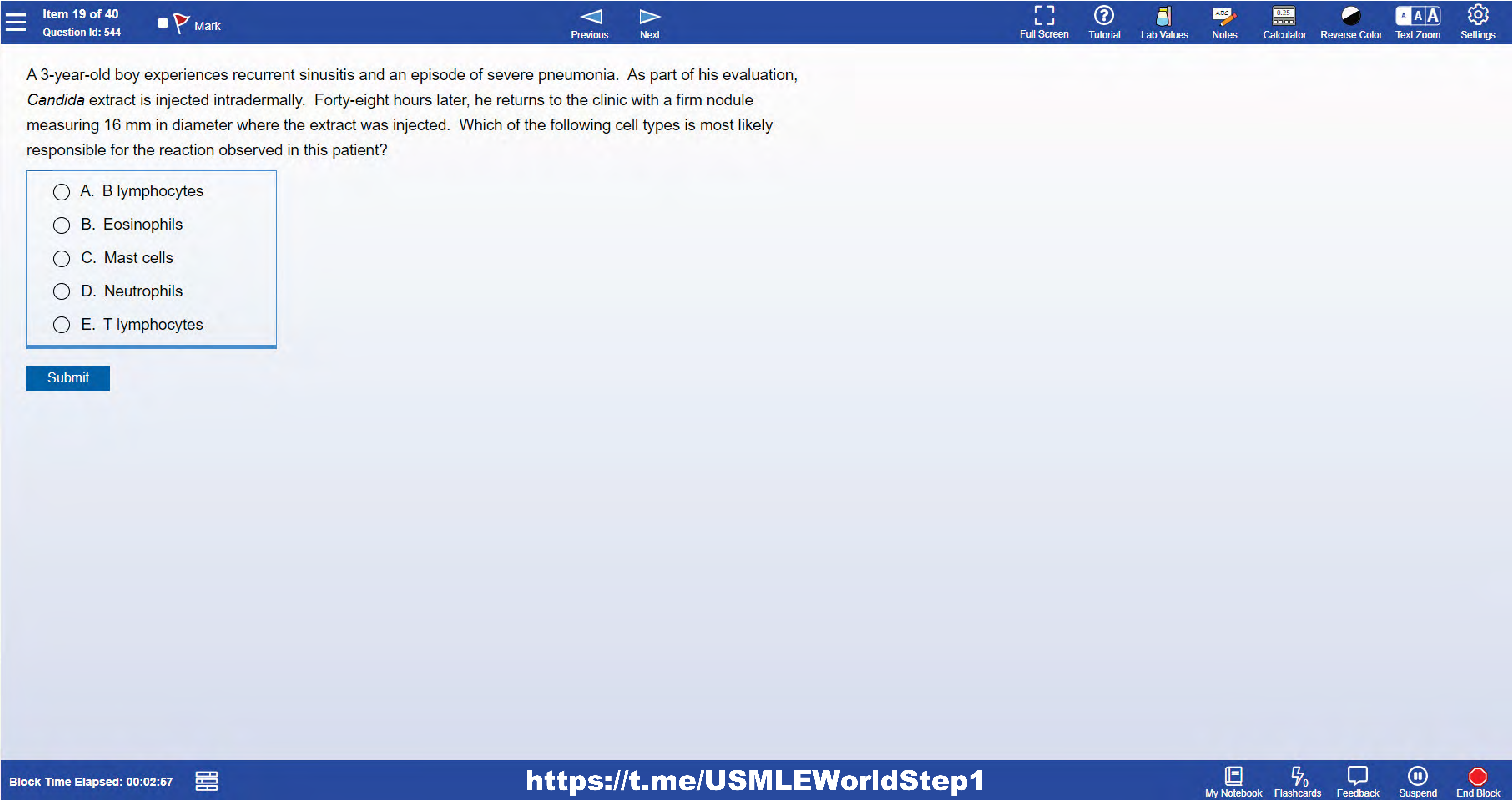
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A 3-year-old boy experiences recurrent sinusitis and an episode of severe pneumonia. As part of his evaluation, *Candida* extract is injected intradermally. Forty-eight hours later, he returns to the clinic with a firm nodule measuring 16 mm in diameter where the extract was injected. Which of the following cell types is most likely responsible for the reaction observed in this patient?

○ A. B lymphocytes
○ B. Eosinophils
○ C. Mast cells
○ D. Neutrophils
○ E. T lymphocytes

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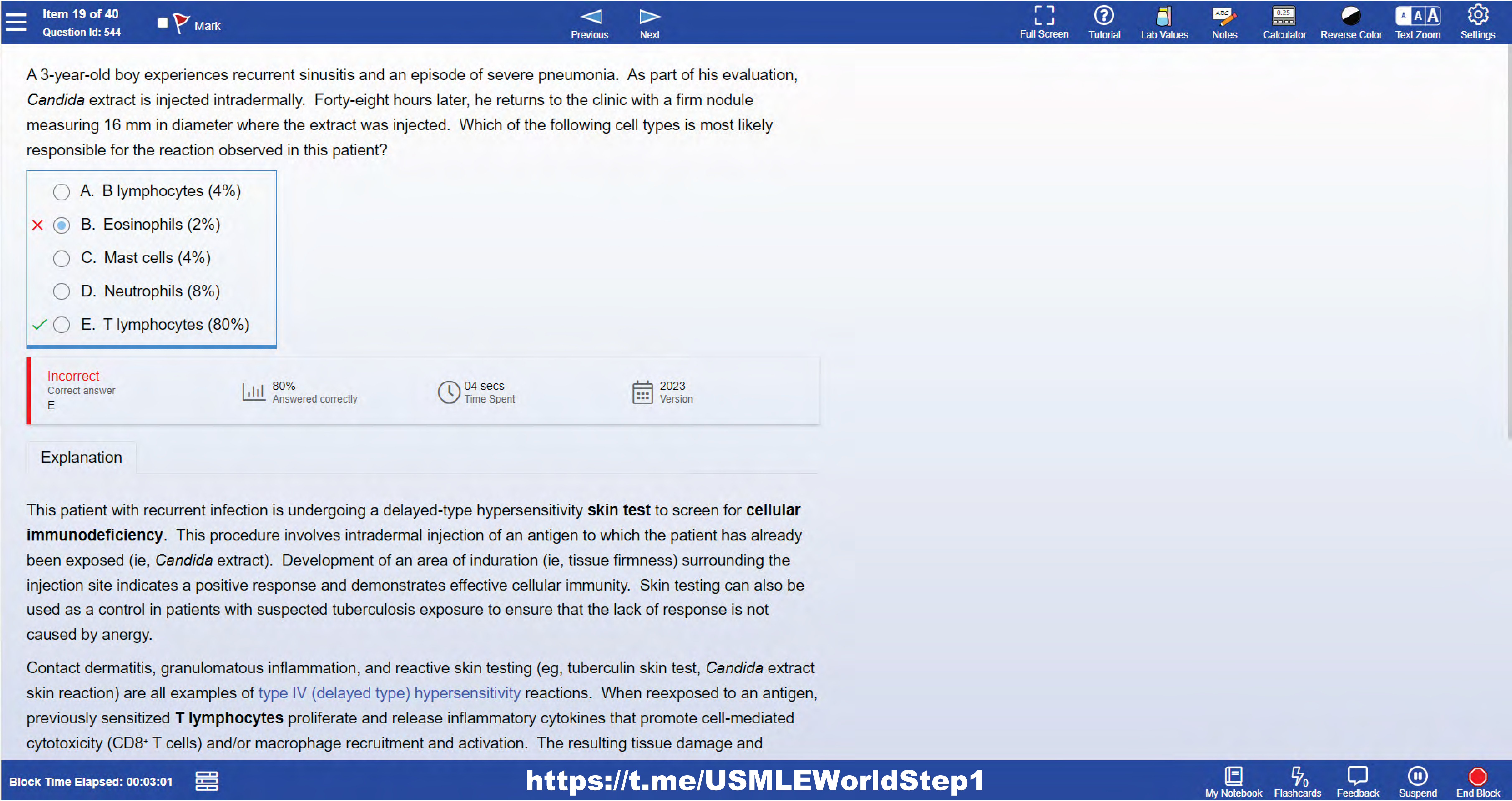
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- ○ A. B lymphocytes (4%)
- ✗ ● B. Eosinophils (2%)
- ○ C. Mast cells (4%)
- ○ D. Neutrophils (8%)
- ✓ ○ E. T lymphocytes (80%)

Incorrect Correct answer E	80% Answered correctly	04 secs Time Spent	2023 Version

Explanation

This patient with recurrent infection is undergoing a delayed-type hypersensitivity **skin test** to screen for **cellular immunodeficiency**. This procedure involves intradermal injection of an antigen to which the patient has already been exposed (ie, *Candida* extract). Development of an area of induration (ie, tissue firmness) surrounding the injection site indicates a positive response and demonstrates effective cellular immunity. Skin testing can also be used as a control in patients with suspected tuberculosis exposure to ensure that the lack of response is not caused by anergy.

Contact dermatitis, granulomatous inflammation, and reactive skin testing (eg, tuberculin skin test, *Candida* extract skin reaction) are all examples of type IV (delayed type) hypersensitivity reactions. When reexposed to an antigen, previously sensitized **T lymphocytes** proliferate and release inflammatory cytokines that promote cell-mediated cytotoxicity ($CD8^+$ T cells) and/or macrophage recruitment and activation. The resulting tissue damage and

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(Choice A) Antibody production by activated B lymphocytes (eg, plasma cells) plays a central role in type I, II, and III hypersensitivity reactions. The timeframe of these reactions can be immediate (type I: eg, anaphylaxis, allergies) or variable (types II and III: eg, most autoimmune disorders, serum sickness).

(Choice B) Eosinophils are phagocytic cells that play a role in the defense against parasitic organisms. These cells are present in small numbers in the bloodstream but are often found in increased numbers in the affected tissues of patients with type I hypersensitivity responses (eg, asthma, allergies).

(Choice C) Mast cells are granulocytes that are the primary mediators of type I (immediate) hypersensitivity reactions (eg, allergies). Sensitized mast cells degranulate and release inflammatory mediators (eg, histamine, prostaglandins) when allergen-specific IgE cross-link on the mast cell Fc receptors, causing rapid swelling and tissue damage.

(Choice D) Neutrophils are the primary phagocytes of the innate immune system and play an ancillary role in some hypersensitivity reactions. Neutrophil deficiency or dysfunction can lead to severe infections without evidence of a significant immune response (eg, pus, infiltrates, erythema).

Educational objective:

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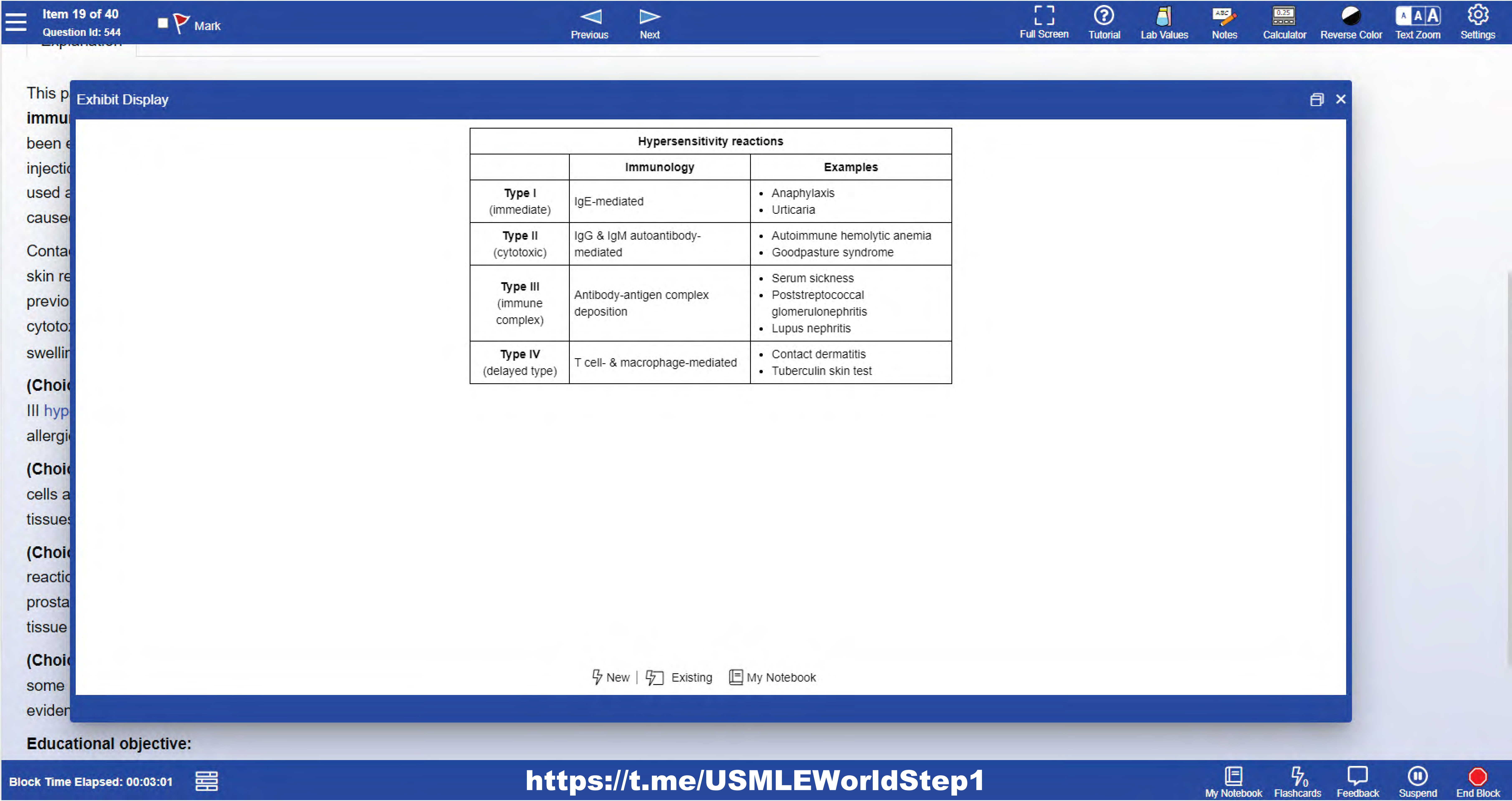
Educational objective:
Type IV (delayed) hypersensitivity reactions (eg, *Candida* extract skin test, contact dermatitis) are characterized by erythema and induration that develops 24-48 hours after repeat exposure to an antigen. T lymphocytes mediate the inflammation in these reactions through cytokine release, $CD8^+$ cytotoxicity, and macrophage recruitment.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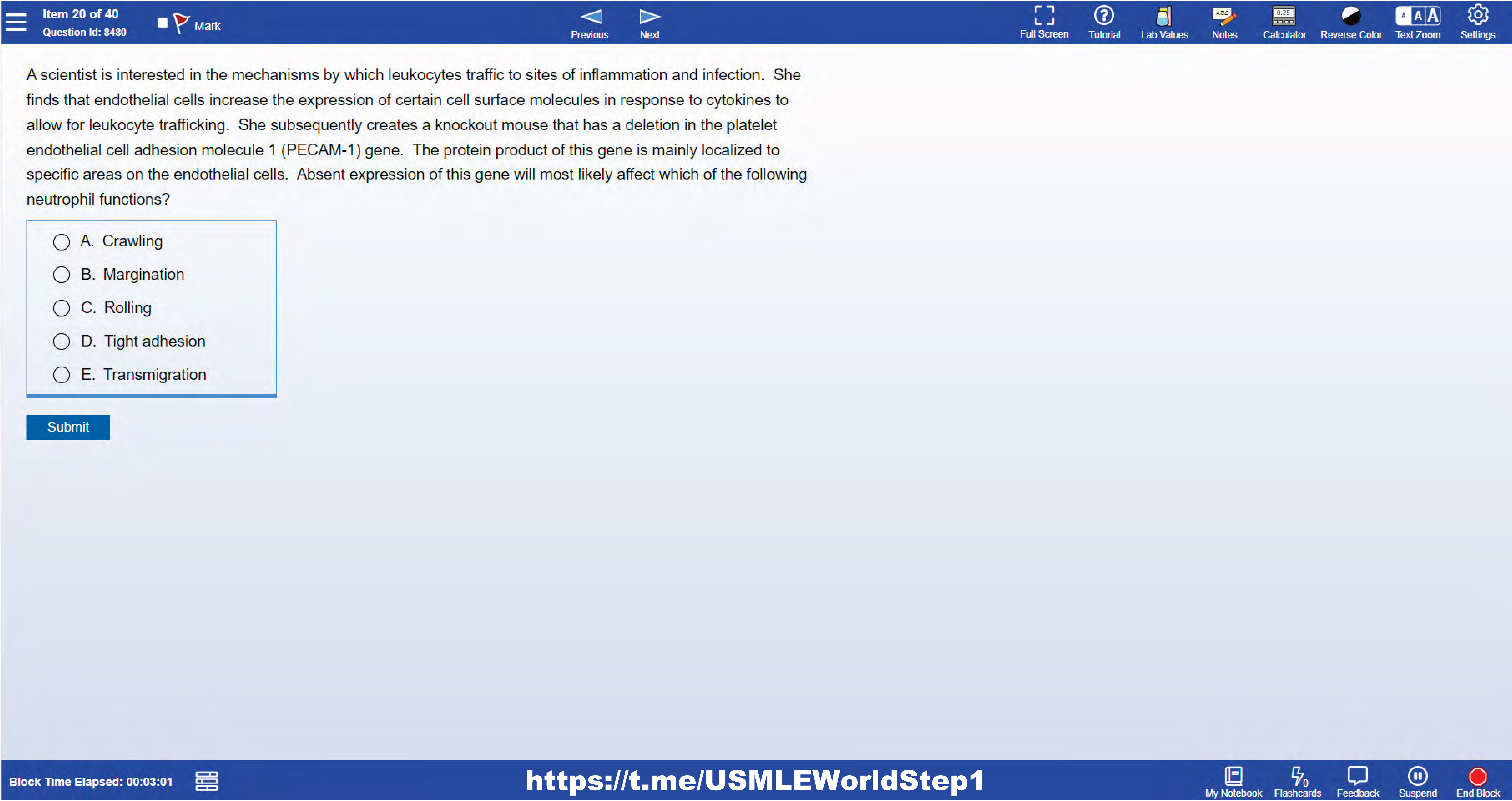
Educational objective:

Hypersensitivity reactions		
	Immunology	**Examples**
Type I (immediate)	IgE-mediated	• Anaphylaxis • Urticaria
Type II (cytotoxic)	IgG & IgM autoantibody-mediated	• Autoimmune hemolytic anemia • Goodpasture syndrome
Type III (immune complex)	Antibody-antigen complex deposition	• Serum sickness • Poststreptococcal glomerulonephritis • Lupus nephritis
Type IV (delayed type)	T cell- & macrophage-mediated	• Contact dermatitis • Tuberculin skin test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Item 20 of 40
Question Id: 8480

A scientist is interested in the mechanisms by which leukocytes traffic to sites of inflammation and infection. She finds that endothelial cells increase the expression of certain cell surface molecules in response to cytokines to allow for leukocyte trafficking. She subsequently creates a knockout mouse that has a deletion in the platelet endothelial cell adhesion molecule 1 (PECAM-1) gene. The protein product of this gene is mainly localized to specific areas on the endothelial cells. Absent expression of this gene will most likely affect which of the following neutrophil functions?

○ A. Crawling
○ B. Margination
○ C. Rolling
○ D. Tight adhesion
○ E. Transmigration

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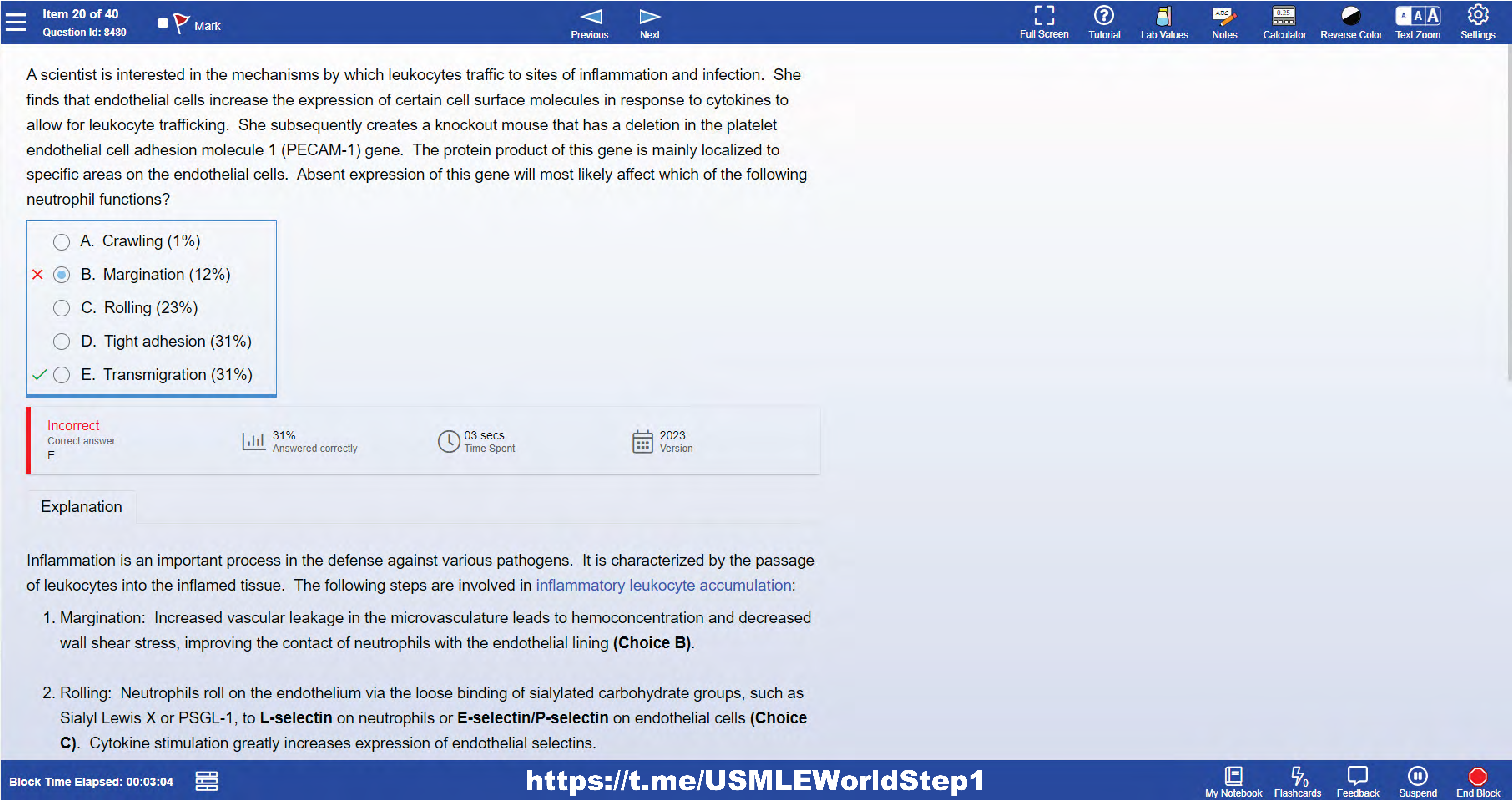
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○ A. Crawling (1%)
✗ ● B. Margination (12%)
○ C. Rolling (23%)
○ D. Tight adhesion (31%)
✓ ○ E. Transmigration (31%)

Incorrect
Correct answer
E

31%
Answered correctly

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Explanation

Inflammation is an important process in the defense against various pathogens. It is characterized by the passage of leukocytes into the inflamed tissue. The following steps are involved in inflammatory leukocyte accumulation:

1. Margination: Increased vascular leakage in the microvasculature leads to hemoconcentration and decreased wall shear stress, improving the contact of neutrophils with the endothelial lining **(Choice B)**.

2. Rolling: Neutrophils roll on the endothelium via the loose binding of sialylated carbohydrate groups, such as Sialyl Lewis X or PSGL-1, to **L-selectin** on neutrophils or **E-selectin/P-selectin** on endothelial cells **(Choice C)**. Cytokine stimulation greatly increases expression of endothelial selectins.

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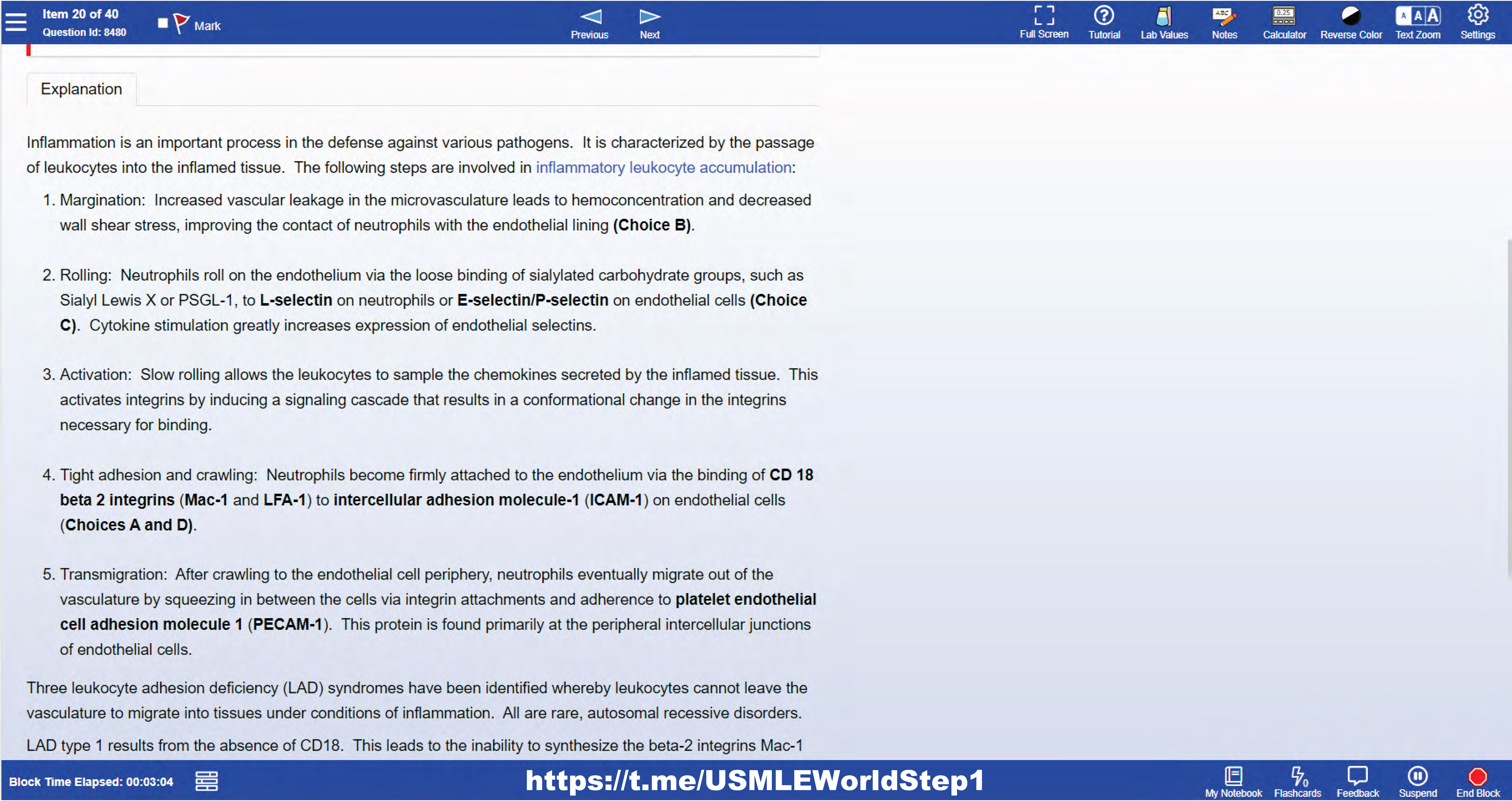
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3. Activation: Slow rolling allows the leukocytes to sample the chemokines secreted by the inflamed tissue. This activates integrins by inducing a signaling cascade that results in a conformational change in the integrins necessary for binding.

4. Tight adhesion and crawling: Neutrophils become firmly attached to the endothelium via the binding of **CD 18 beta 2 integrins** (**Mac-1** and **LFA-1**) to **intercellular adhesion molecule-1** (**ICAM-1**) on endothelial cells (**Choices A and D)**.

5. Transmigration: After crawling to the endothelial cell periphery, neutrophils eventually migrate out of the vasculature by squeezing in between the cells via integrin attachments and adherence to **platelet endothelial cell adhesion molecule 1** (**PECAM-1**). This protein is found primarily at the peripheral intercellular junctions of endothelial cells.

Three leukocyte adhesion deficiency (LAD) syndromes have been identified whereby leukocytes cannot leave the vasculature to migrate into tissues under conditions of inflammation. All are rare, autosomal recessive disorders.

LAD type 1 results from the absence of CD18. This leads to the inability to synthesize the beta-2 integrins Mac-1

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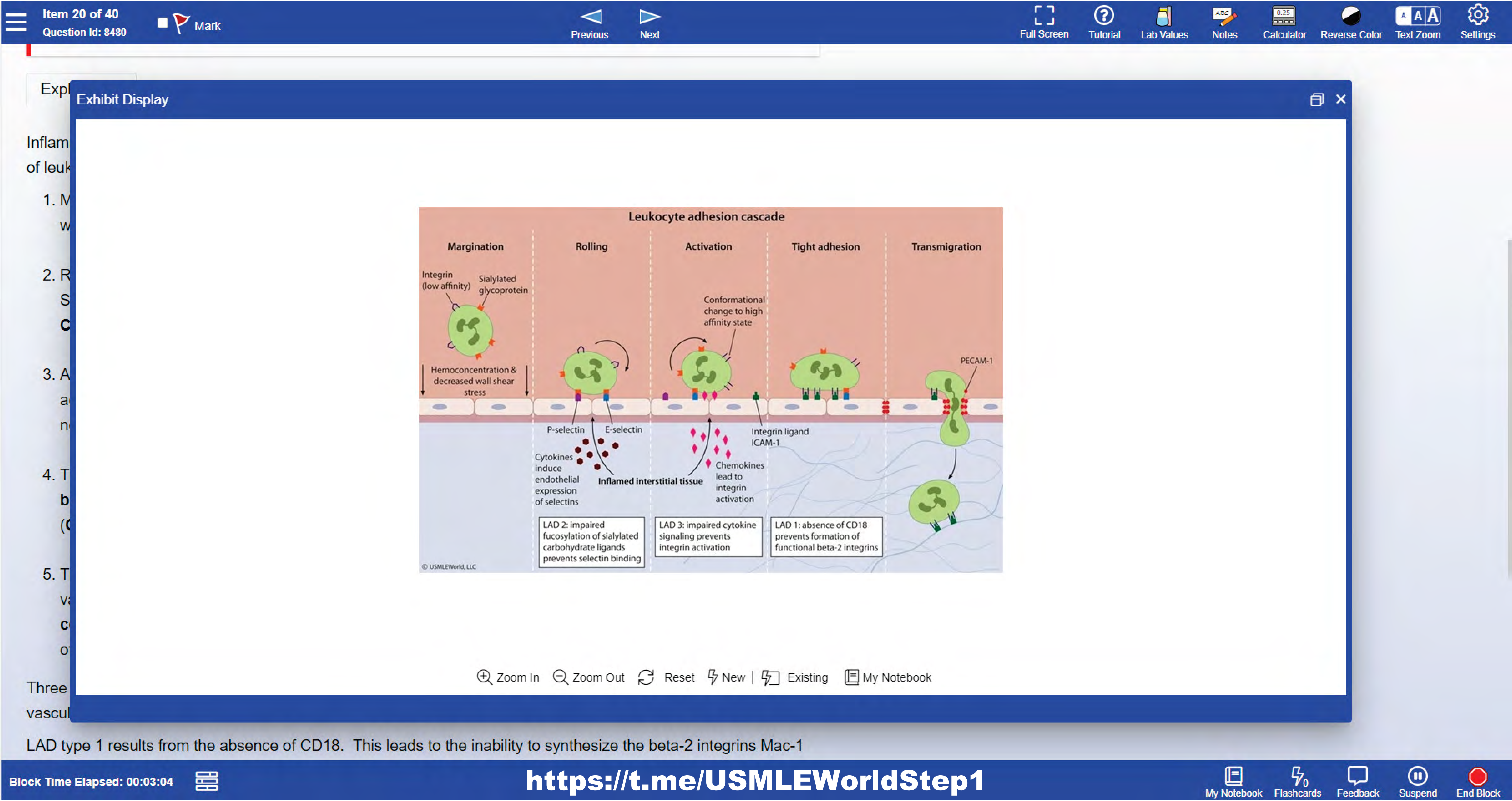
LAD type 1 results from the absence of CD18. This leads to the inability to synthesize the beta-2 integrins Mac-1 and LFA1, affecting tight adhesion, crawling, and transmigration. The clinical manifestations include recurrent skin infections **without pus formation**, **delayed detachment of the umbilical cord**, and poor wound healing. LAD type 2 is a milder condition, with no delay in the separation of the umbilical cord and less severe and fewer infections. LAD type 3 is similar to type 1 and causes severe, recurrent bacterial infections, delayed separation of the umbilical cord, and bleeding complications (due to affected beta-3 integrins on platelets).

Educational objective:
Inflammation is characterized by the passage of circulating inflammatory leukocytes into the inflamed tissue. The steps involved include margination, rolling, activation, tight adhesion and crawling, and transmigration.

References



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Leukocyte adhesion cascade

Margination
Rolling
Activation
Tight adhesion
Transmigration
Integrin (low affinity)
Sialylated glycoprotein
Hemoconcentration & decreased wall shear stress
Conformational change to high affinity state
PECAM-1
P-selectin
E-selectin
Integrin ligand ICAM-1
Cytokines induce endothelial expression of selectins
Inflamed interstitial tissue
Chemokines lead to integrin activation

LAD 2: impaired fucosylation of sialylated carbohydrate ligands prevents selectin binding

LAD 3: impaired cytokine signaling prevents integrin activation

LAD 1: absence of CD18 prevents formation of functional beta-2 integrins

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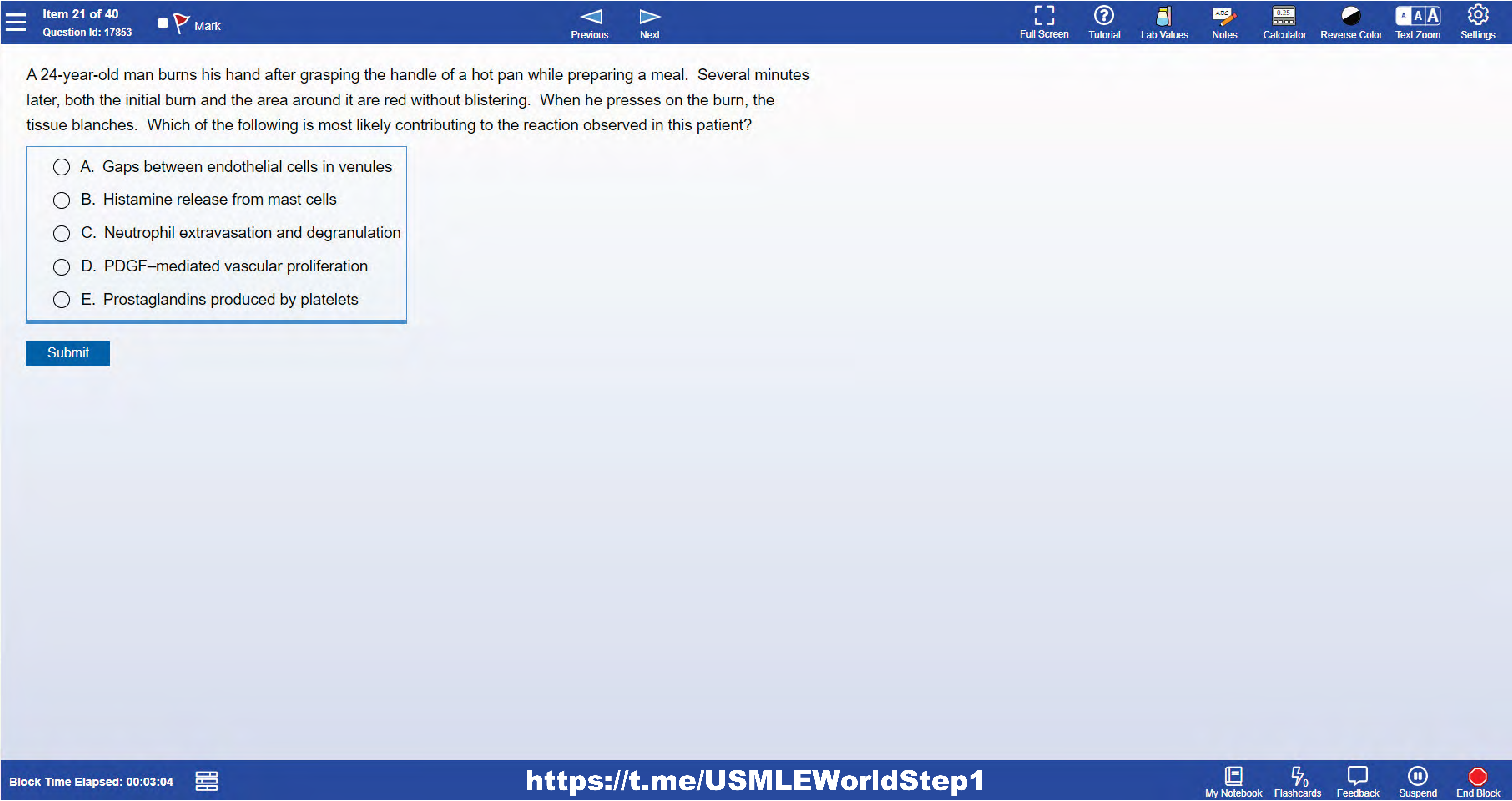
LAD type 1 results from the absence of CD18. This leads to the inability to synthesize the beta-2 integrins Mac-1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Question Id: 17853

A 24-year-old man burns his hand after grasping the handle of a hot pan while preparing a meal. Several minutes later, both the initial burn and the area around it are red without blistering. When he presses on the burn, the tissue blanches. Which of the following is most likely contributing to the reaction observed in this patient?

○ A. Gaps between endothelial cells in venules
○ B. Histamine release from mast cells
○ C. Neutrophil extravasation and degranulation
○ D. PDGF–mediated vascular proliferation
○ E. Prostaglandins produced by platelets

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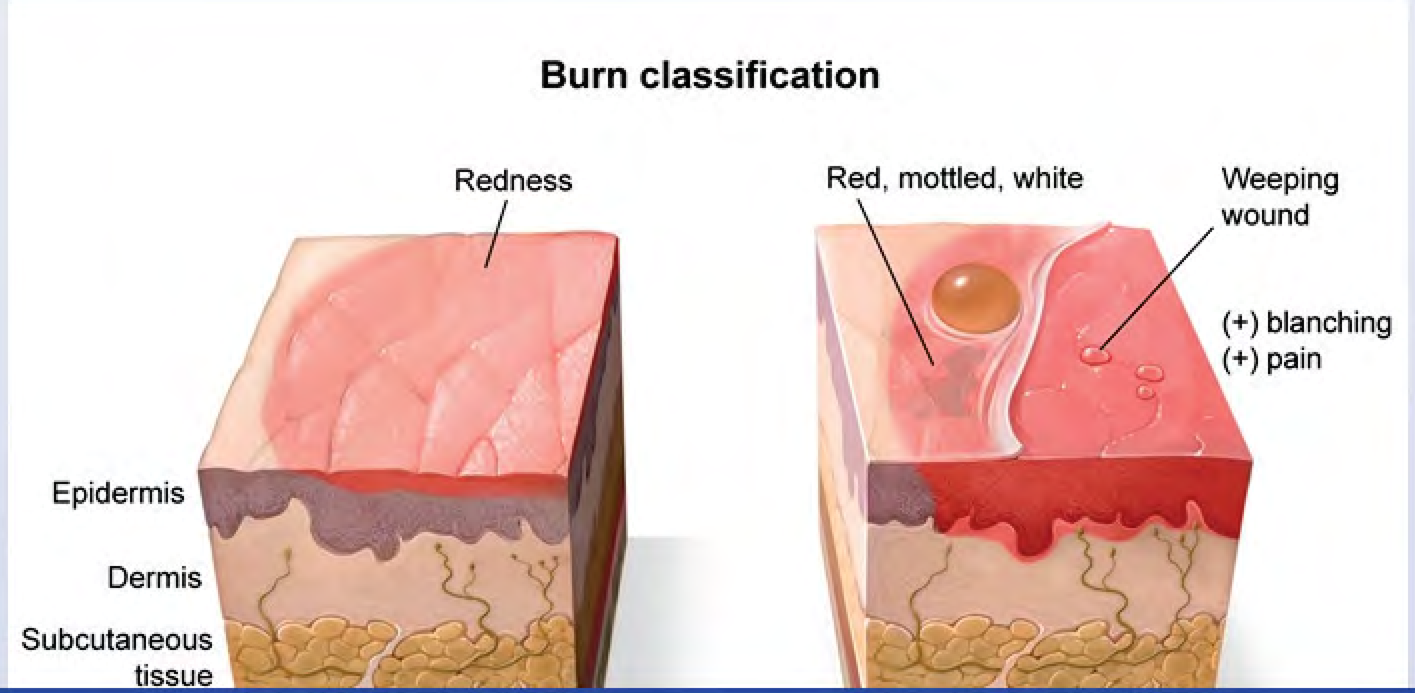
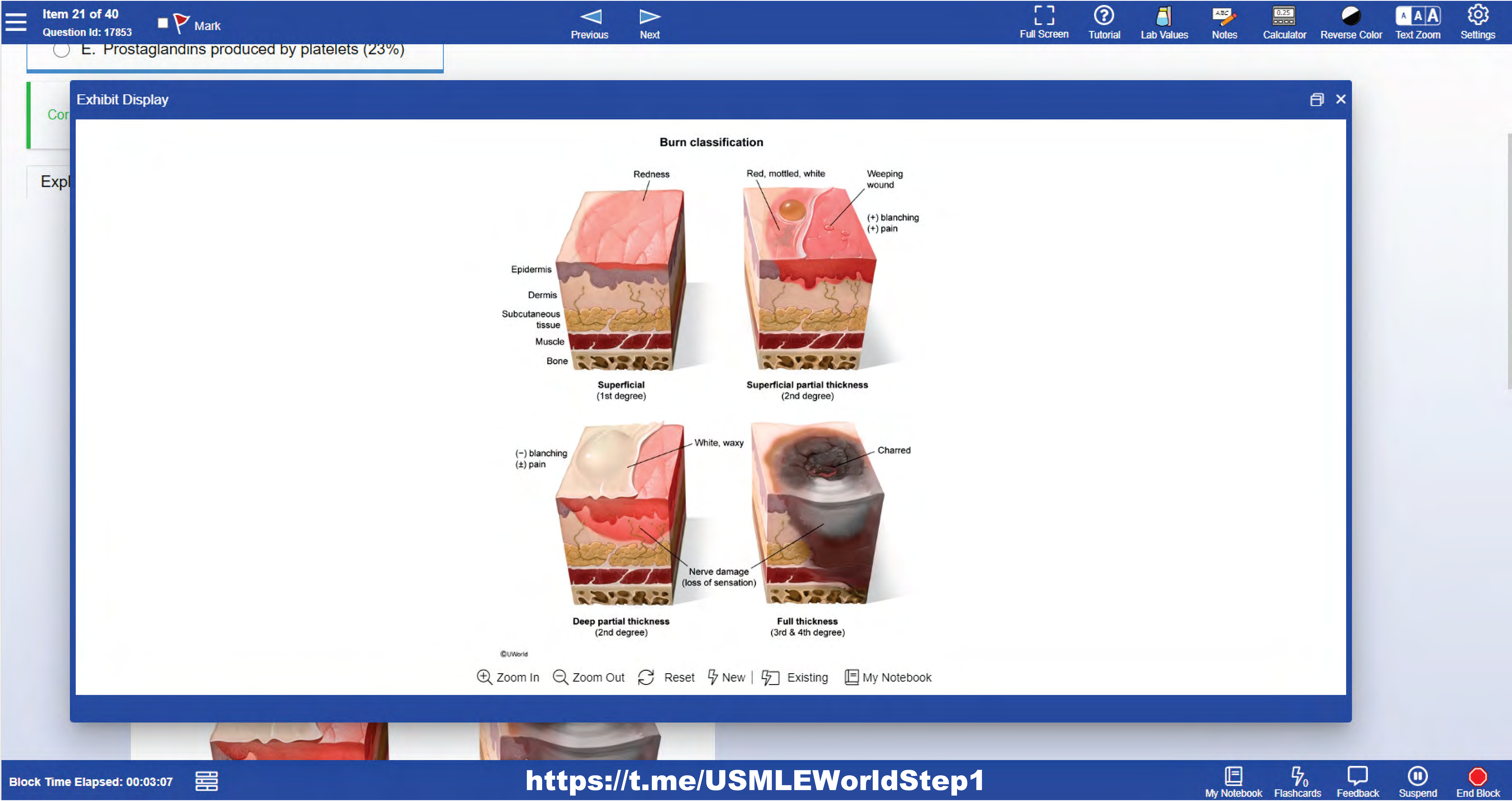
- ○ A. Gaps between endothelial cells in venules (35%)
- ✓ ● B. Histamine release from mast cells (26%)
- ○ C. Neutrophil extravasation and degranulation (7%)
- ○ D. PDGF–mediated vascular proliferation (6%)
- ○ E. Prostaglandins produced by platelets (23%)

Correct	26% Answered correctly	03 secs Time Spent	2023 Version

Explanation


Burn classification
Redness
Red, mottled, white
Weeping wound
(+) blanching
(+) pain
Epidermis
Dermis
Subcutaneous tissue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○ E. Prostaglandins produced by platelets (23%)

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Burn classification

Redness
Epidermis
Dermis
Subcutaneous tissue
Muscle
Bone
Superficial
(1st degree)
Red, mottled, white
Weeping wound
(+) blanching
(+) pain
Superficial partial thickness
(2nd degree)
(−) blanching
(±) pain
White, waxy
Nerve damage
(loss of sensation)
Deep partial thickness
(2nd degree)
Charred
Full thickness
(3rd & 4th degree)
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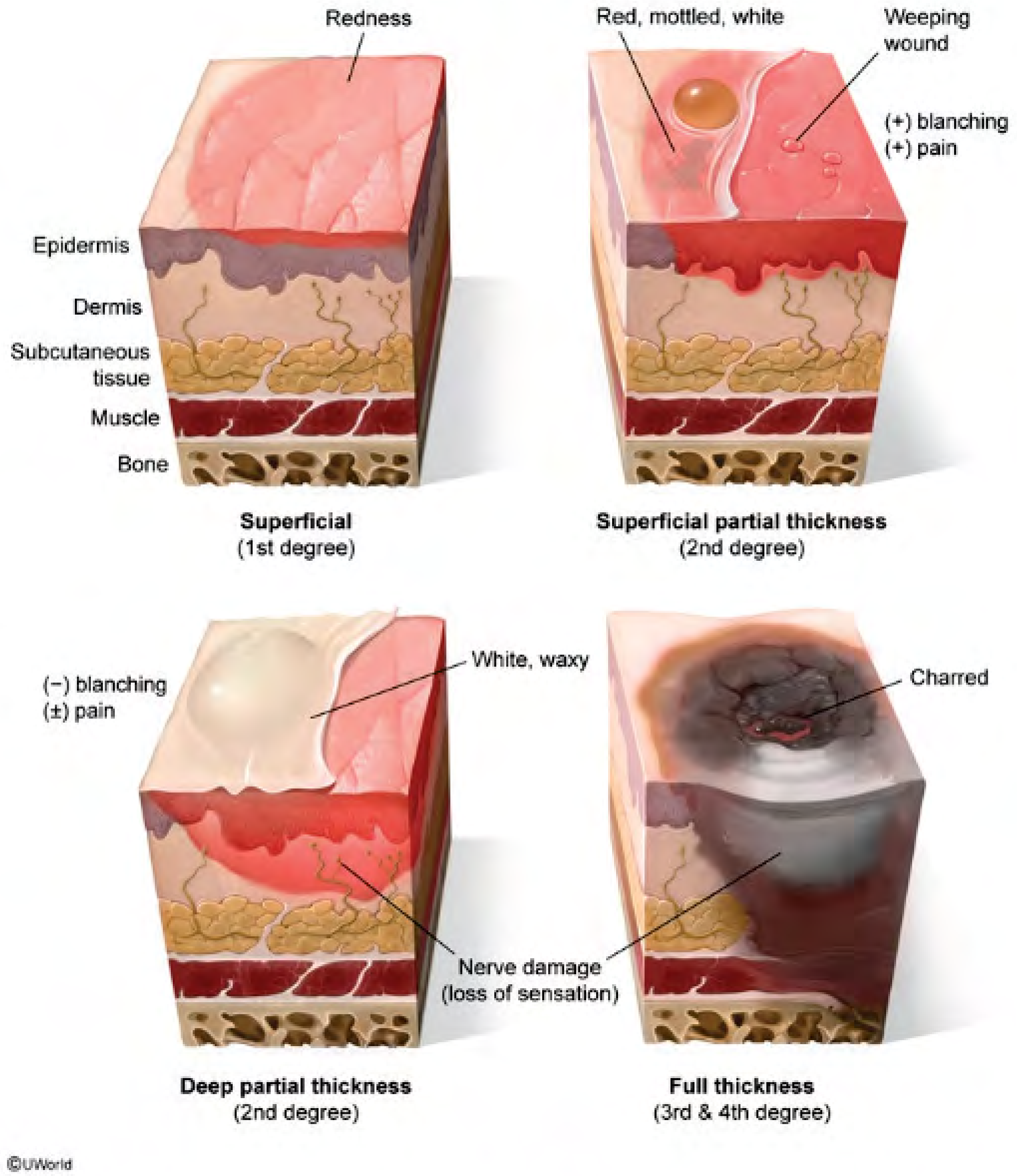
Burn classification


Redness
Red, mottled, white
Weeping wound
(+) blanching
(+) pain
Epidermis
Dermis
Subcutaneous tissue
Muscle
Bone
(−) blanching
(±) pain
White, waxy
Charred
Nerve damage (loss of sensation)
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Superficial
(1st degree)

Superficial partial thickness
(2nd degree)

Deep partial thickness
(2nd degree)

Full thickness
(3rd & 4th degree)

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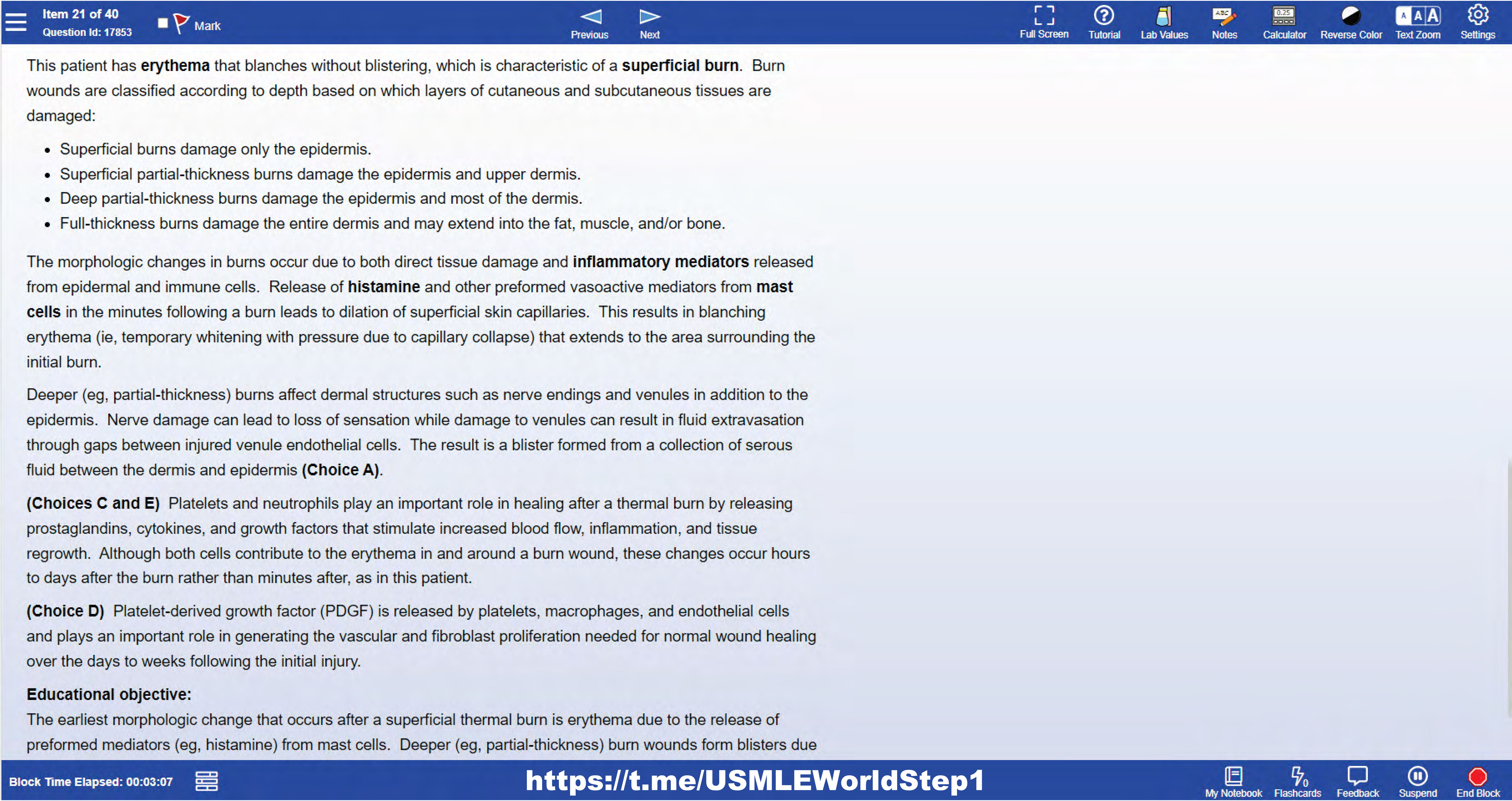
cells in the minutes following a burn leads to dilation of superficial skin capillaries. This results in blanching erythema (ie, temporary whitening with pressure due to capillary collapse) that extends to the area surrounding the



This patient has **erythema** that blanches without blistering, which is characteristic of a **superficial burn**. Burn wounds are classified according to depth based on which layers of cutaneous and subcutaneous tissues are damaged:

- Superficial burns damage only the epidermis.
- Superficial partial-thickness burns damage the epidermis and upper dermis.
- Deep partial-thickness burns damage the epidermis and most of the dermis.
- Full-thickness burns damage the entire dermis and may extend into the fat, muscle, and/or bone.

The morphologic changes in burns occur due to both direct tissue damage and **inflammatory mediators** released from epidermal and immune cells. Release of **histamine** and other preformed vasoactive mediators from **mast cells** in the minutes following a burn leads to dilation of superficial skin capillaries. This results in blanching erythema (ie, temporary whitening with pressure due to capillary collapse) that extends to the area surrounding the initial burn.

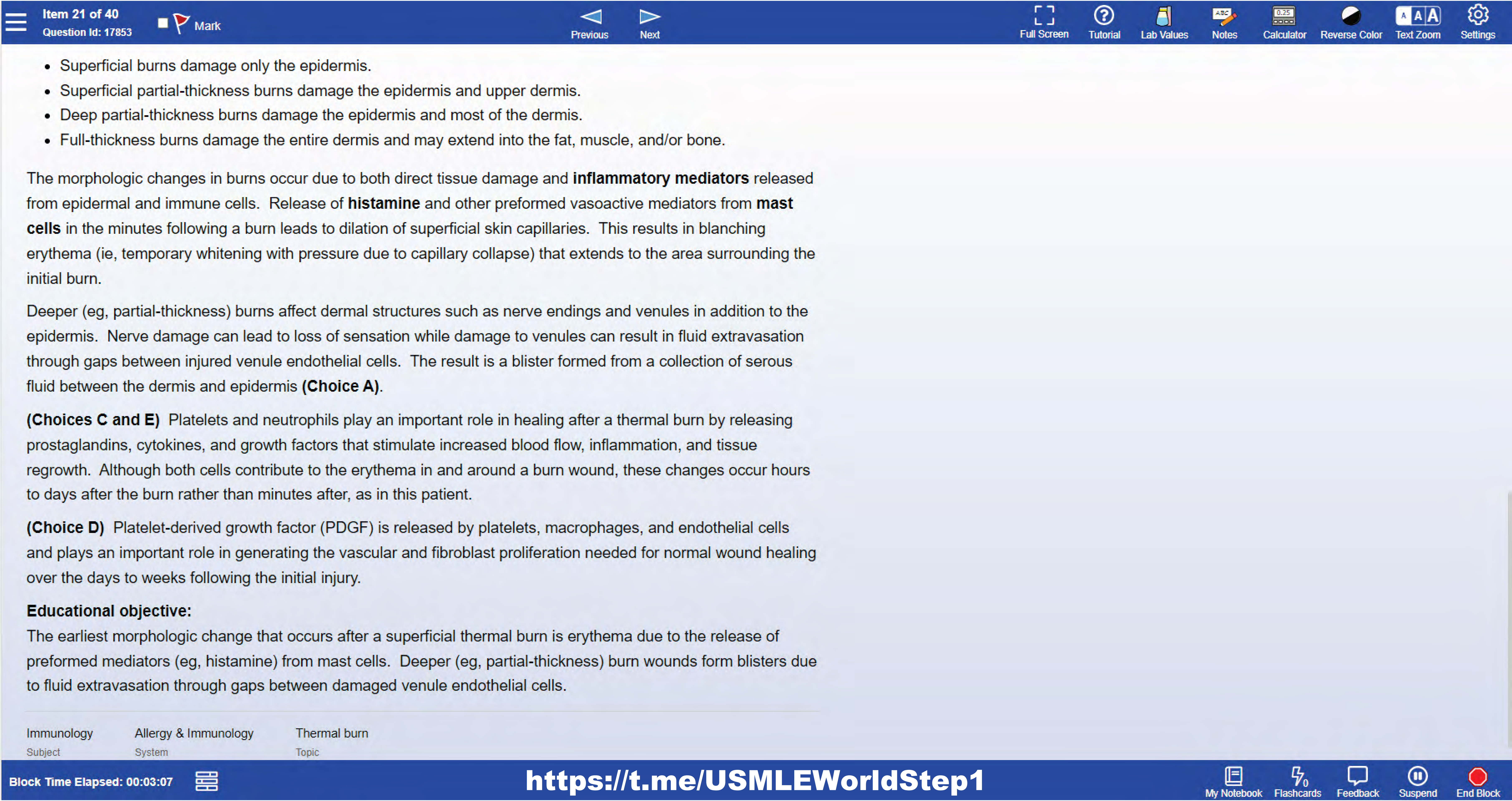
Deeper (eg, partial-thickness) burns affect dermal structures such as nerve endings and venules in addition to the epidermis. Nerve damage can lead to loss of sensation while damage to venules can result in fluid extravasation through gaps between injured venule endothelial cells. The result is a blister formed from a collection of serous fluid between the dermis and epidermis **(Choice A)**.

(Choices C and E) Platelets and neutrophils play an important role in healing after a thermal burn by releasing prostaglandins, cytokines, and growth factors that stimulate increased blood flow, inflammation, and tissue regrowth. Although both cells contribute to the erythema in and around a burn wound, these changes occur hours to days after the burn rather than minutes after, as in this patient.

(Choice D) Platelet-derived growth factor (PDGF) is released by platelets, macrophages, and endothelial cells and plays an important role in generating the vascular and fibroblast proliferation needed for normal wound healing over the days to weeks following the initial injury.

Educational objective:

The earliest morphologic change that occurs after a superficial thermal burn is erythema due to the release of preformed mediators (eg, histamine) from mast cells. Deeper (eg, partial-thickness) burn wounds form blisters due



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Question Id: 17853

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Immunology	Allergy & Immunology	Thermal burn
Subject	System	Topic

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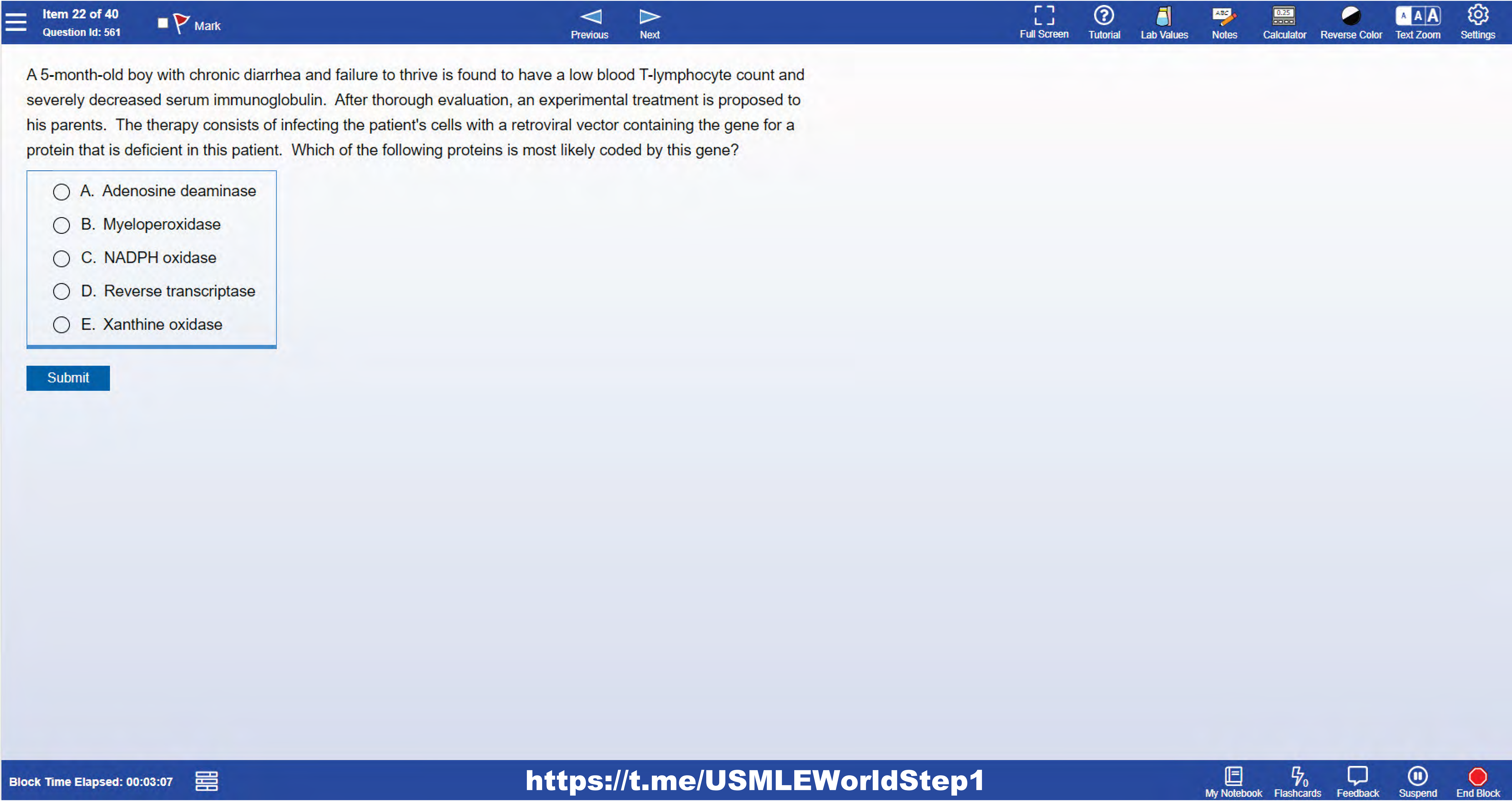
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Item 22 of 40
Question Id: 561

A 5-month-old boy with chronic diarrhea and failure to thrive is found to have a low blood T-lymphocyte count and severely decreased serum immunoglobulin. After thorough evaluation, an experimental treatment is proposed to his parents. The therapy consists of infecting the patient's cells with a retroviral vector containing the gene for a protein that is deficient in this patient. Which of the following proteins is most likely coded by this gene?

○ A. Adenosine deaminase
○ B. Myeloperoxidase
○ C. NADPH oxidase
○ D. Reverse transcriptase
○ E. Xanthine oxidase

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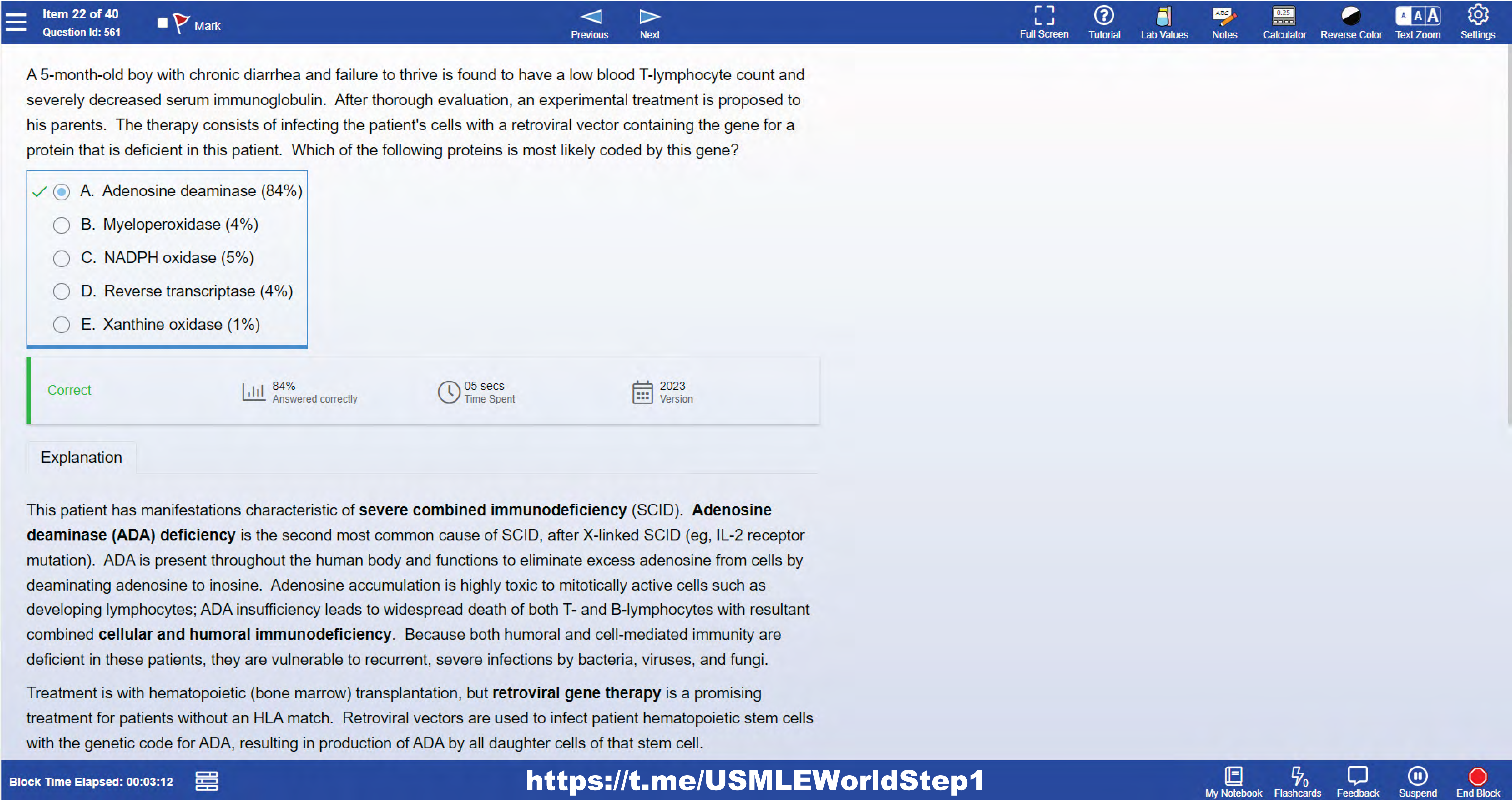
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✓ ● A. Adenosine deaminase (84%)
○ B. Myeloperoxidase (4%)
○ C. NADPH oxidase (5%)
○ D. Reverse transcriptase (4%)
○ E. Xanthine oxidase (1%)

Correct

84%
Answered correctly

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Explanation

This patient has manifestations characteristic of **severe combined immunodeficiency** (SCID). **Adenosine deaminase (ADA) deficiency** is the second most common cause of SCID, after X-linked SCID (eg, IL-2 receptor mutation). ADA is present throughout the human body and functions to eliminate excess adenosine from cells by deaminating adenosine to inosine. Adenosine accumulation is highly toxic to mitotically active cells such as developing lymphocytes; ADA insufficiency leads to widespread death of both T- and B-lymphocytes with resultant combined **cellular and humoral immunodeficiency**. Because both humoral and cell-mediated immunity are deficient in these patients, they are vulnerable to recurrent, severe infections by bacteria, viruses, and fungi.

Treatment is with hematopoietic (bone marrow) transplantation, but **retroviral gene therapy** is a promising treatment for patients without an HLA match. Retroviral vectors are used to infect patient hematopoietic stem cells with the genetic code for ADA, resulting in production of ADA by all daughter cells of that stem cell.

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This patient has manifestations characteristic of **severe combined immunodeficiency** (SCID). **Adenosine deaminase (ADA) deficiency** is the second most common cause of SCID, after X-linked SCID (eg, IL-2 receptor mutation). ADA is present throughout the human body and functions to eliminate excess adenosine from cells by deaminating adenosine to inosine. Adenosine accumulation is highly toxic to mitotically active cells such as developing lymphocytes; ADA insufficiency leads to widespread death of both T- and B-lymphocytes with resultant combined **cellular and humoral immunodeficiency**. Because both humoral and cell-mediated immunity are deficient in these patients, they are vulnerable to recurrent, severe infections by bacteria, viruses, and fungi.

Treatment is with hematopoietic (bone marrow) transplantation, but **retroviral gene therapy** is a promising treatment for patients without an HLA match. Retroviral vectors are used to infect patient hematopoietic stem cells with the genetic code for ADA, resulting in production of ADA by all daughter cells of that stem cell.

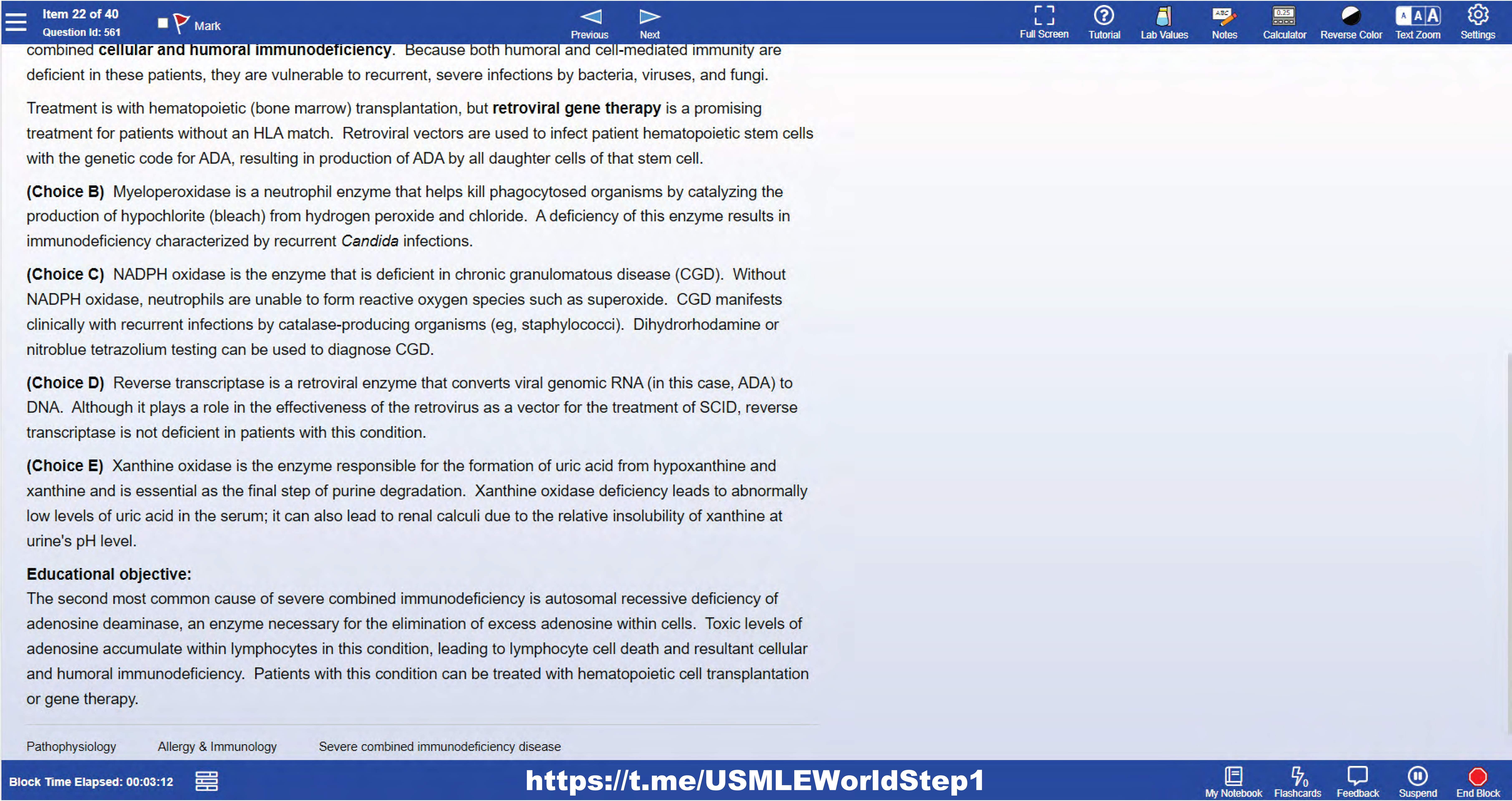
(Choice B) Myeloperoxidase is a neutrophil enzyme that helps kill phagocytosed organisms by catalyzing the production of hypochlorite (bleach) from hydrogen peroxide and chloride. A deficiency of this enzyme results in immunodeficiency characterized by recurrent *Candida* infections.

(Choice C) NADPH oxidase is the enzyme that is deficient in chronic granulomatous disease (CGD). Without NADPH oxidase, neutrophils are unable to form reactive oxygen species such as superoxide. CGD manifests clinically with recurrent infections by catalase-producing organisms (eg, staphylococci). Dihydrorhodamine or nitroblue tetrazolium testing can be used to diagnose CGD.

(Choice D) Reverse transcriptase is a retroviral enzyme that converts viral genomic RNA (in this case, ADA) to DNA. Although it plays a role in the effectiveness of the retrovirus as a vector for the treatment of SCID, reverse transcriptase is not deficient in patients with this condition.

(Choice E) Xanthine oxidase is the enzyme responsible for the formation of uric acid from hypoxanthine and xanthine and is essential as the final step of purine degradation. Xanthine oxidase deficiency leads to abnormally low levels of uric acid in the serum; it can also lead to renal calculi due to the relative insolubility of xanthine at urine's pH level.

Educational objective:



combined **cellular and humoral immunodeficiency**. Because both humoral and cell-mediated immunity are deficient in these patients, they are vulnerable to recurrent, severe infections by bacteria, viruses, and fungi.

Treatment is with hematopoietic (bone marrow) transplantation, but **retroviral gene therapy** is a promising treatment for patients without an HLA match. Retroviral vectors are used to infect patient hematopoietic stem cells with the genetic code for ADA, resulting in production of ADA by all daughter cells of that stem cell.

(Choice B) Myeloperoxidase is a neutrophil enzyme that helps kill phagocytosed organisms by catalyzing the production of hypochlorite (bleach) from hydrogen peroxide and chloride. A deficiency of this enzyme results in immunodeficiency characterized by recurrent *Candida* infections.

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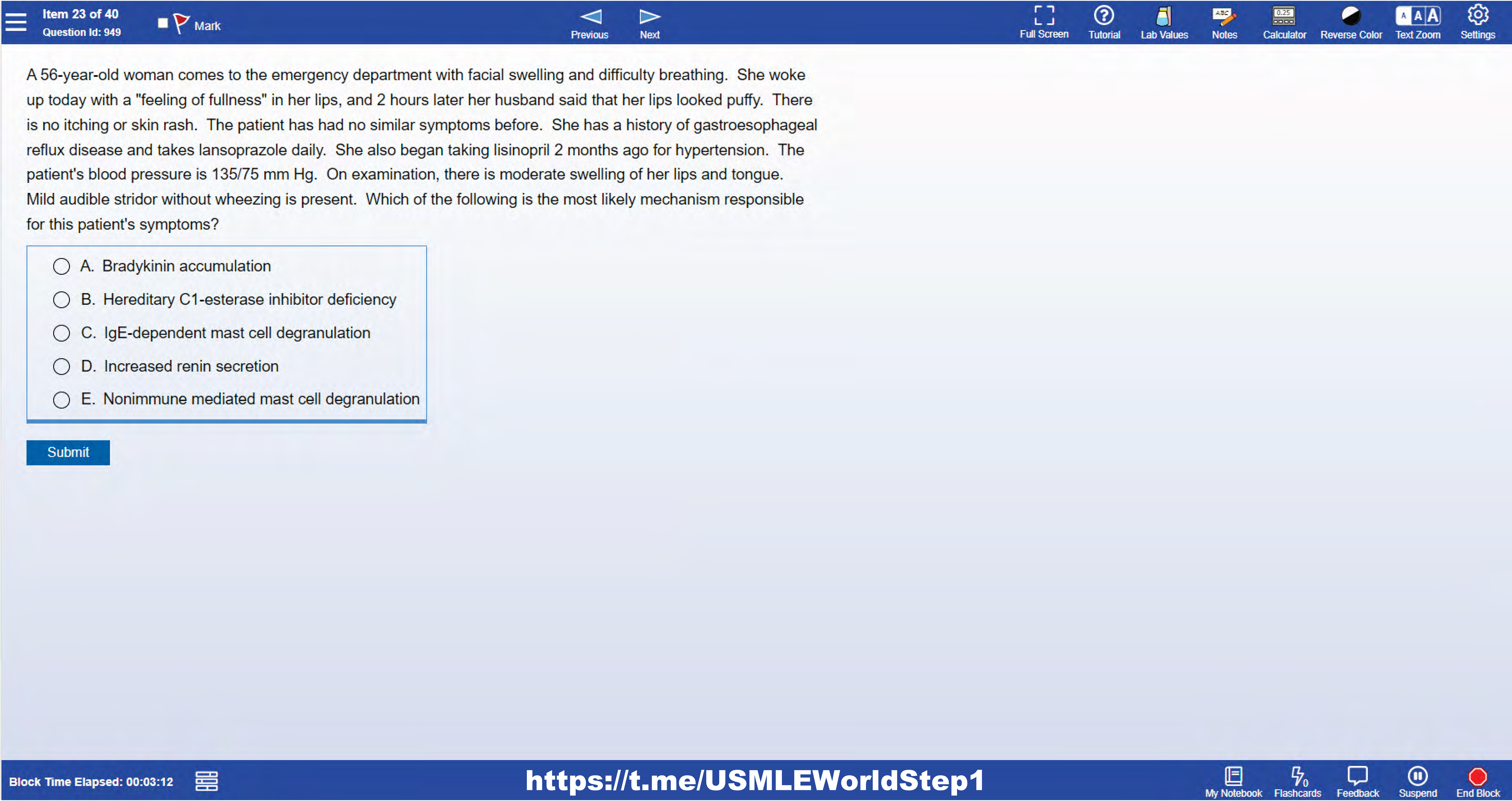
Educational objective:

The second most common cause of severe combined immunodeficiency is autosomal recessive deficiency of adenosine deaminase, an enzyme necessary for the elimination of excess adenosine within cells. Toxic levels of adenosine accumulate within lymphocytes in this condition, leading to lymphocyte cell death and resultant cellular and humoral immunodeficiency. Patients with this condition can be treated with hematopoietic cell transplantation or gene therapy.

Pathophysiology   Allergy & Immunology   Severe combined immunodeficiency disease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A 56-year-old woman comes to the emergency department with facial swelling and difficulty breathing. She woke up today with a "feeling of fullness" in her lips, and 2 hours later her husband said that her lips looked puffy. There is no itching or skin rash. The patient has had no similar symptoms before. She has a history of gastroesophageal reflux disease and takes lansoprazole daily. She also began taking lisinopril 2 months ago for hypertension. The patient's blood pressure is 135/75 mm Hg. On examination, there is moderate swelling of her lips and tongue. Mild audible stridor without wheezing is present. Which of the following is the most likely mechanism responsible for this patient's symptoms?

○ A. Bradykinin accumulation
○ B. Hereditary C1-esterase inhibitor deficiency
○ C. IgE-dependent mast cell degranulation
○ D. Increased renin secretion
○ E. Nonimmune mediated mast cell degranulation

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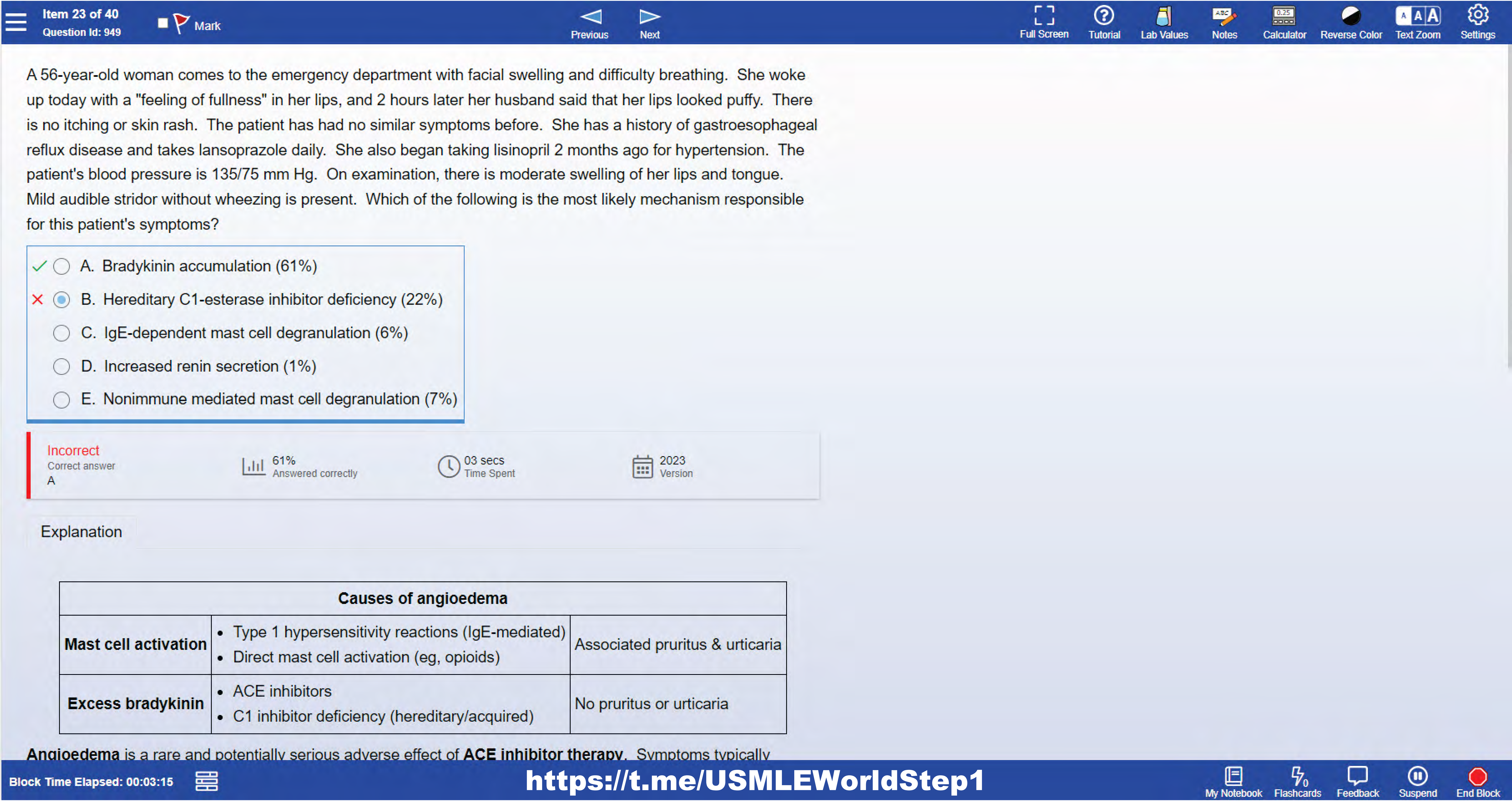
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✓ ○ A. Bradykinin accumulation (61%)
✕ ● B. Hereditary C1-esterase inhibitor deficiency (22%)
○ C. IgE-dependent mast cell degranulation (6%)
○ D. Increased renin secretion (1%)
○ E. Nonimmune mediated mast cell degranulation (7%)

Incorrect
Correct answer
A

61%
Answered correctly

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Explanation

Causes of angioedema		
Mast cell activation	• Type 1 hypersensitivity reactions (IgE-mediated) • Direct mast cell activation (eg, opioids)	Associated pruritus & urticaria
Excess bradykinin	• ACE inhibitors • C1 inhibitor deficiency (hereditary/acquired)	No pruritus or urticaria

Angioedema is a rare and potentially serious adverse effect of **ACE inhibitor therapy**. Symptoms typically

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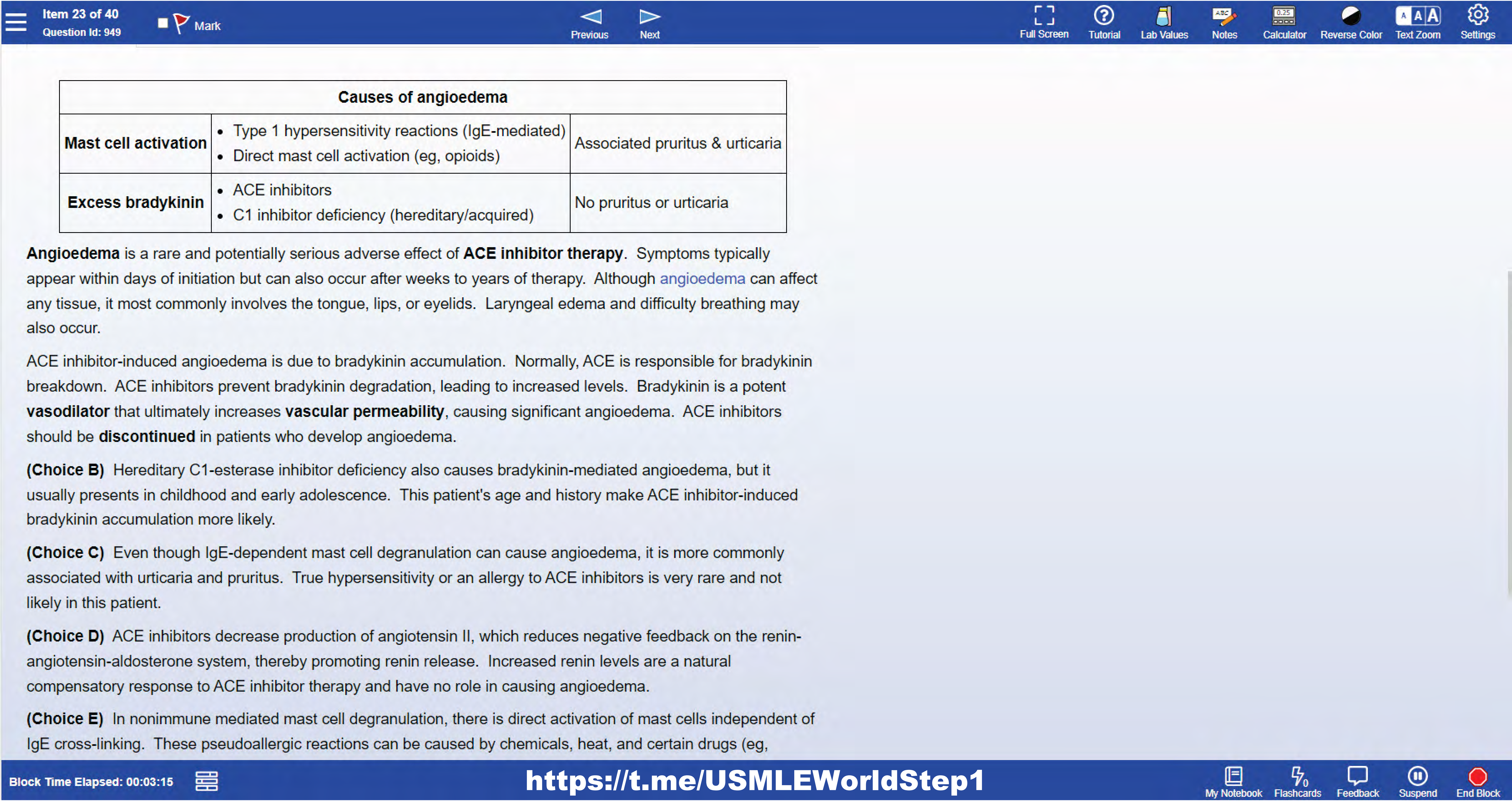

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Mast cell activation	• Type 1 hypersensitivity reactions (IgE-mediated) • Direct mast cell activation (eg, opioids)	Associated pruritus & urticaria
Excess bradykinin	• ACE inhibitors • C1 inhibitor deficiency (hereditary/acquired)	No pruritus or urticaria

Angioedema is a rare and potentially serious adverse effect of **ACE inhibitor therapy**. Symptoms typically appear within days of initiation but can also occur after weeks to years of therapy. Although angioedema can affect any tissue, it most commonly involves the tongue, lips, or eyelids. Laryngeal edema and difficulty breathing may also occur.

ACE inhibitor-induced angioedema is due to bradykinin accumulation. Normally, ACE is responsible for bradykinin breakdown. ACE inhibitors prevent bradykinin degradation, leading to increased levels. Bradykinin is a potent **vasodilator** that ultimately increases **vascular permeability**, causing significant angioedema. ACE inhibitors should be **discontinued** in patients who develop angioedema.

(Choice B) Hereditary C1-esterase inhibitor deficiency also causes bradykinin-mediated angioedema, but it usually presents in childhood and early adolescence. This patient's age and history make ACE inhibitor-induced bradykinin accumulation more likely.

(Choice C) Even though IgE-dependent mast cell degranulation can cause angioedema, it is more commonly associated with urticaria and pruritus. True hypersensitivity or an allergy to ACE inhibitors is very rare and not likely in this patient.

(Choice D) ACE inhibitors decrease production of angiotensin II, which reduces negative feedback on the renin-angiotensin-aldosterone system, thereby promoting renin release. Increased renin levels are a natural compensatory response to ACE inhibitor therapy and have no role in causing angioedema.

(Choice E) In nonimmune mediated mast cell degranulation, there is direct activation of mast cells independent of IgE cross-linking. These pseudoallergic reactions can be caused by chemicals, heat, and certain drugs (eg,

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	• C1 inhibitor deficiency (hereditary/acquired)	

Angioedema is a rare and potentially serious adverse effect of **ACE inhibitor therapy**. Symptoms typically appear within days of initiation but can also occur after weeks to years of therapy. Although angioedema can affect any tissue, it most commonly involves the tongue, lips, or eyelids. Laryngeal edema and difficulty breathing may also occur.

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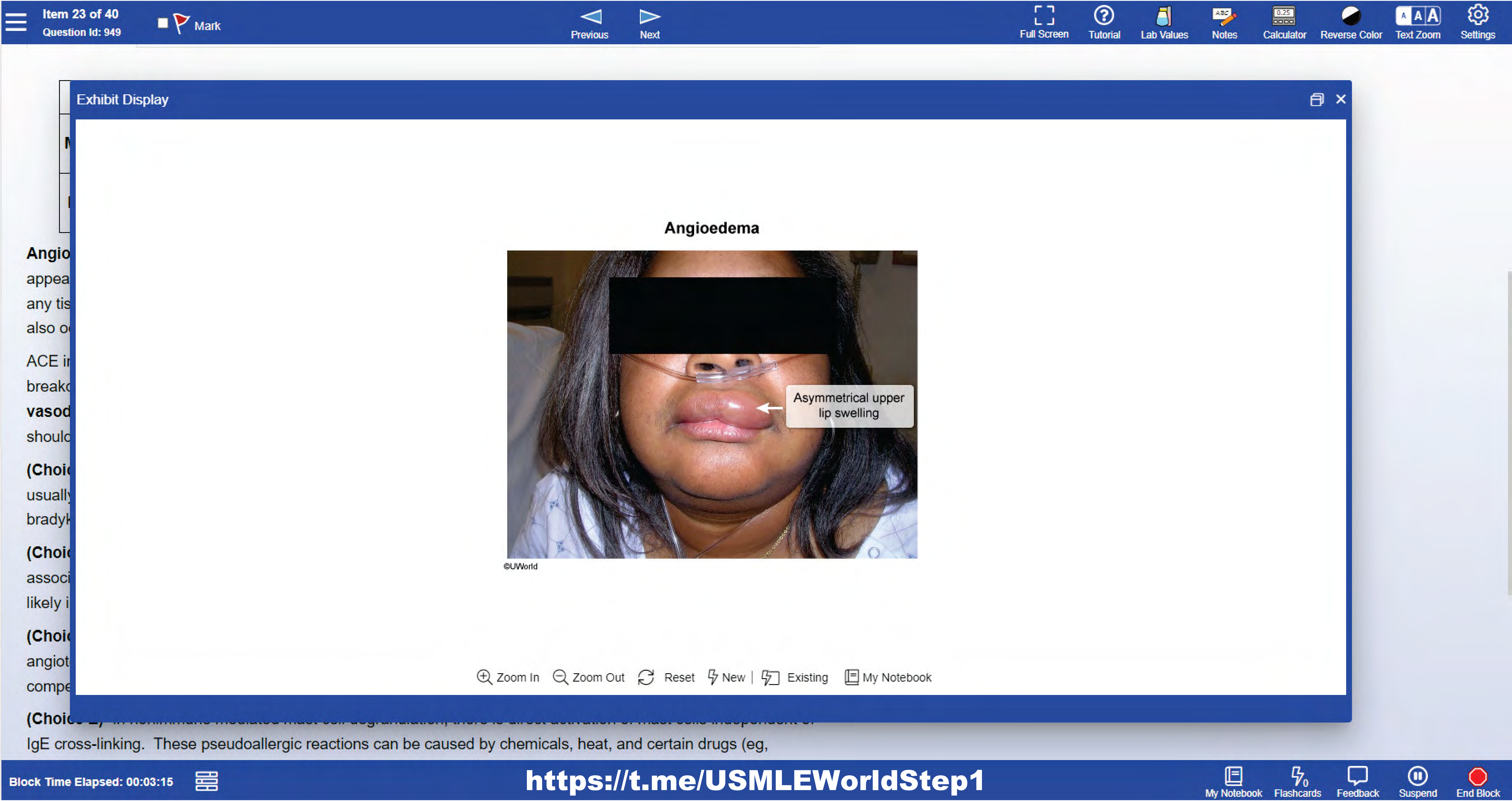
(Choice E) In nonimmune mediated mast cell degranulation, there is direct activation of mast cells independent of IgE cross-linking. These pseudoallergic reactions can be caused by chemicals, heat, and certain drugs (eg, opiates, vancomycin) and are clinically similar to hypersensitivity and allergic reactions.

Educational objective:
Angioedema is a rare and serious adverse effect of ACE inhibitor therapy. ACE inhibition increases bradykinin levels, which increase vascular permeability and lead to angioedema. Symptoms include tongue, lips, or eyelid swelling and, less frequently, laryngeal edema and difficulty breathing. ACE inhibitors should be discontinued in affected patients.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Angioedema

[redacted]

Asymmetrical upper lip swelling

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Question Id: 1612

A 12-year-old girl is being evaluated for recurrent episodes of self-limited colicky abdominal pain and nausea lasting several days. She was also recently hospitalized for an episode of difficulty breathing. The patient has no significant past medical history, but her mother has a history of attacks of severe abdominal pain and diarrhea. Physical examination is unremarkable. Laboratory evaluation reveals decreased serum complement C4 and C1 esterase inhibitor levels. Which of the following drugs is contraindicated in this patient?

○ A. Captopril
○ B. Furosemide
○ C. Methotrexate
○ D. Metoprolol
○ E. Penicillin

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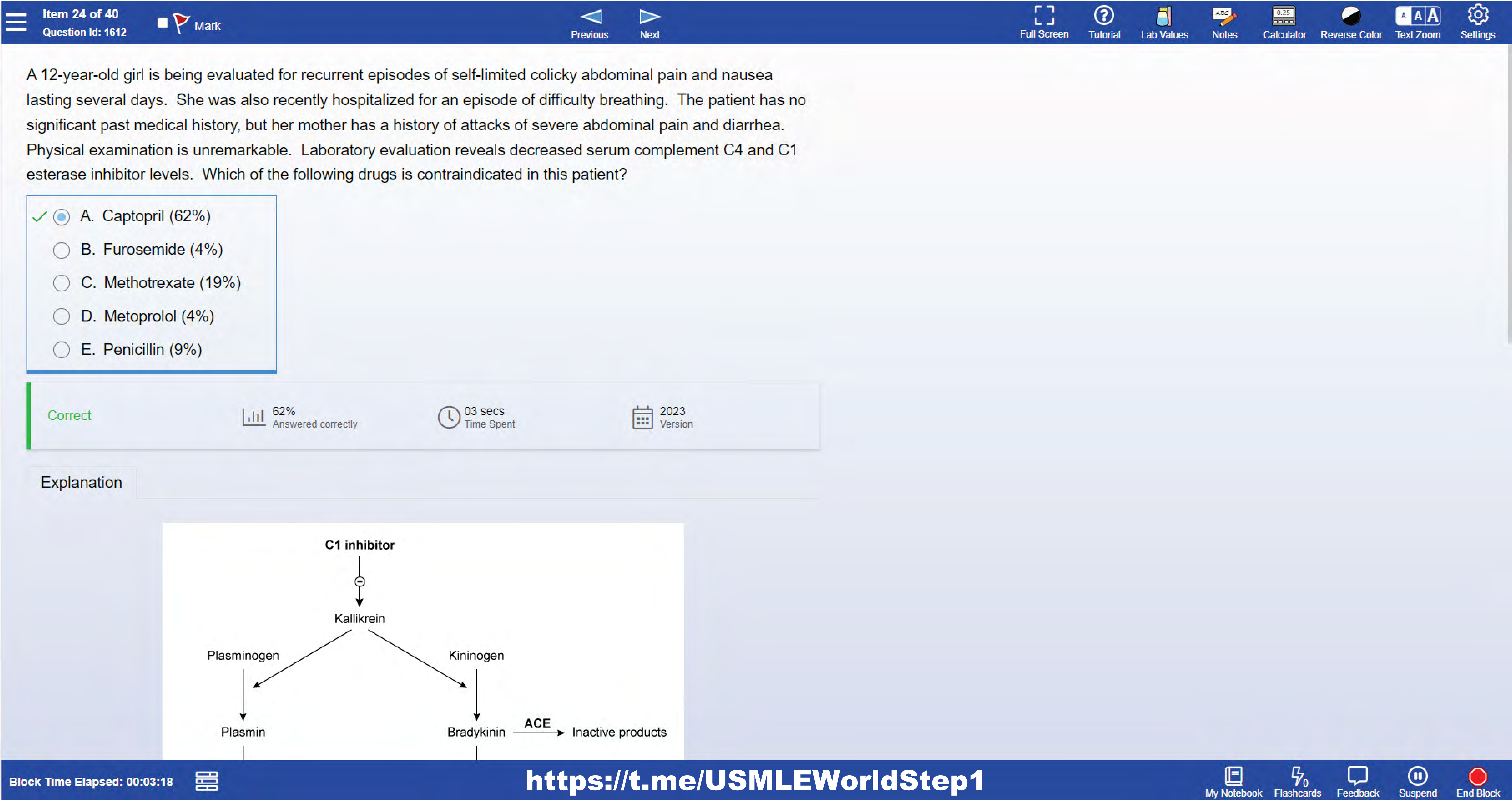
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A 12-year-old girl is being evaluated for recurrent episodes of self-limited colicky abdominal pain and nausea lasting several days. She was also recently hospitalized for an episode of difficulty breathing. The patient has no significant past medical history, but her mother has a history of attacks of severe abdominal pain and diarrhea. Physical examination is unremarkable. Laboratory evaluation reveals decreased serum complement C4 and C1 esterase inhibitor levels. Which of the following drugs is contraindicated in this patient?

✓ ● A. Captopril (62%)
○ B. Furosemide (4%)
○ C. Methotrexate (19%)
○ D. Metoprolol (4%)
○ E. Penicillin (9%)

Correct

62%
Answered correctly

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Explanation

C1 inhibitor
Kallikrein
Plasminogen
Kininogen
Plasmin
Bradykinin
ACE
Inactive products

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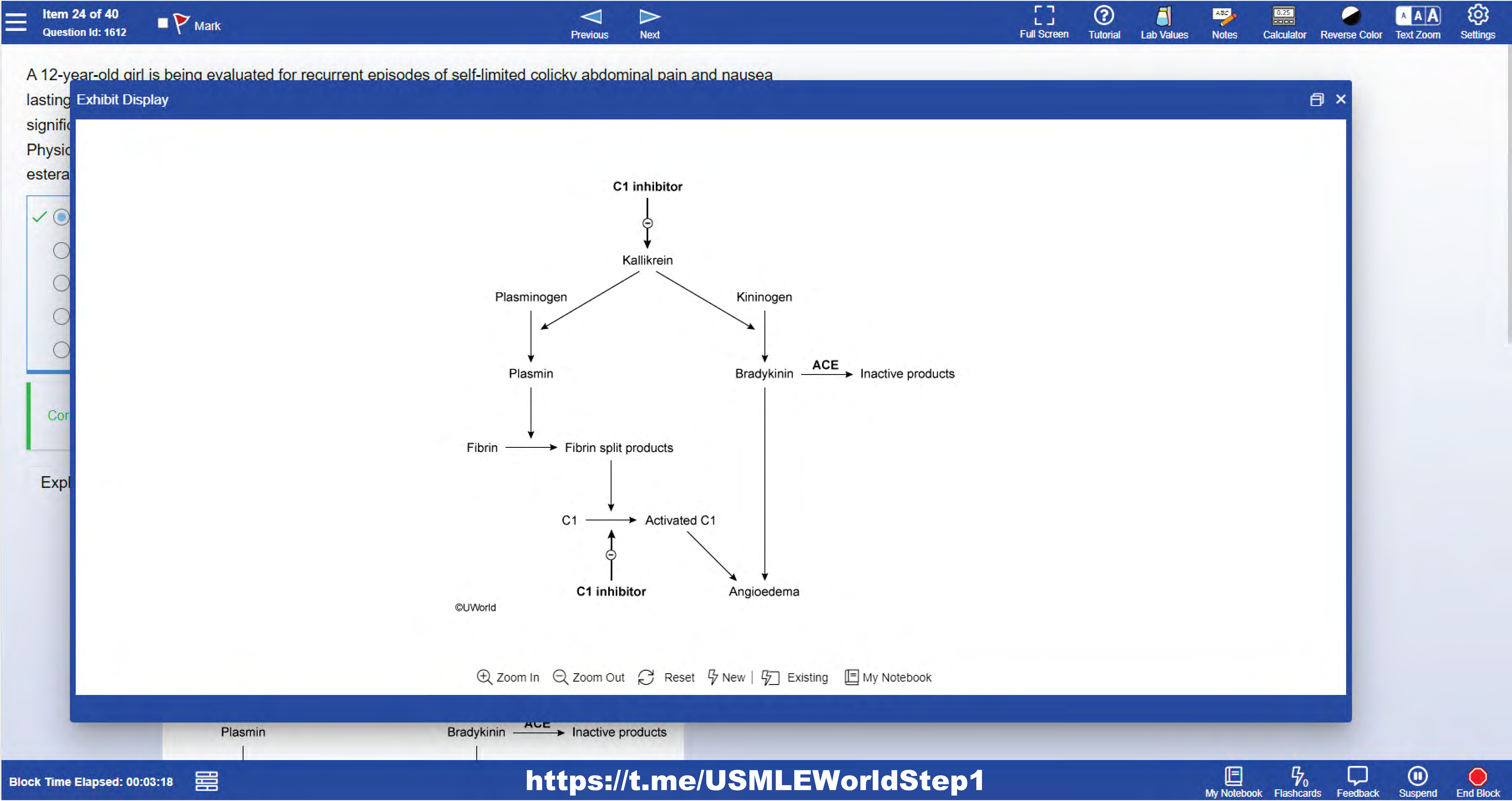
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A 12-year-old girl is being evaluated for recurrent episodes of self-limited colicky abdominal pain and nausea

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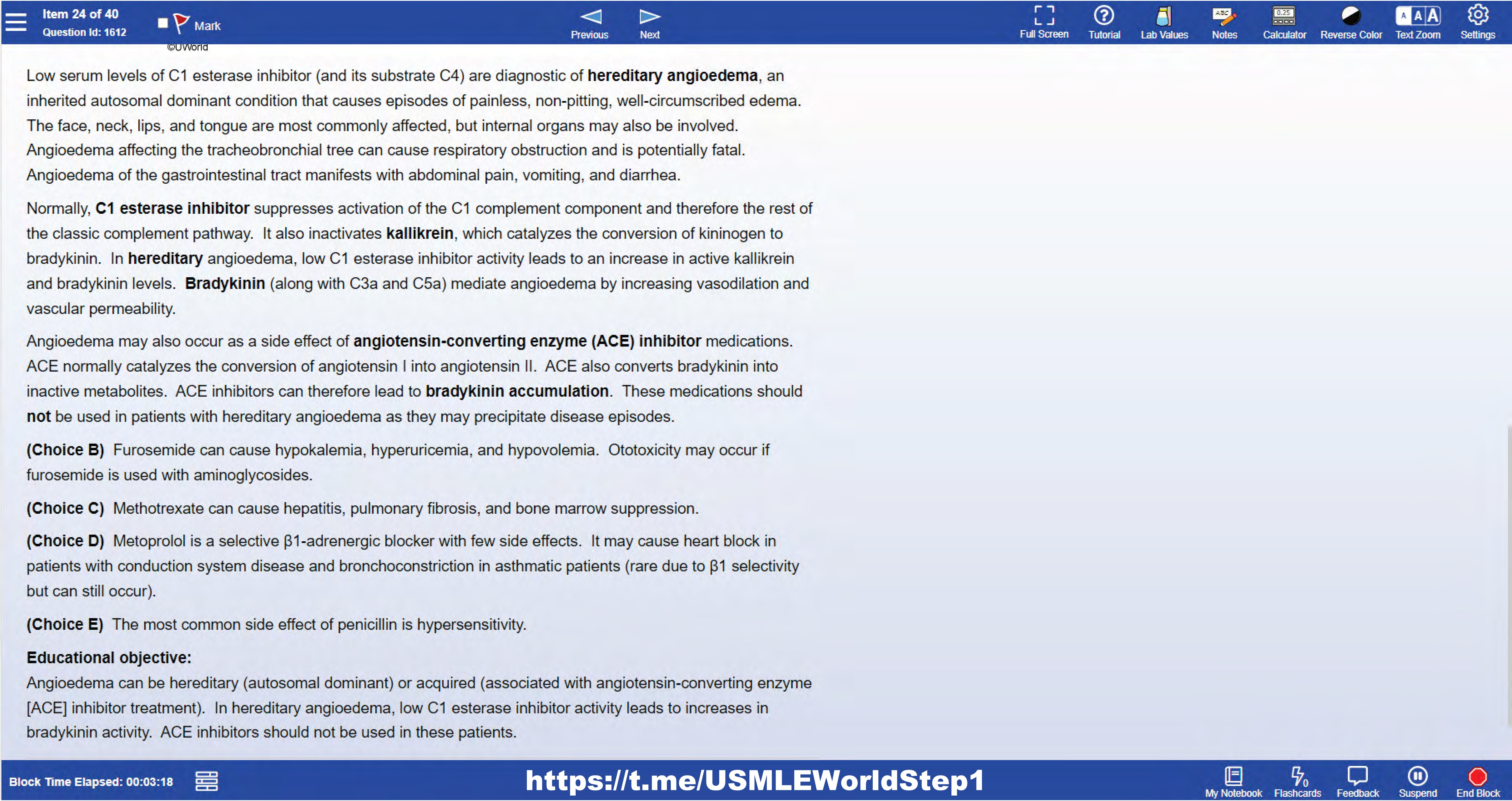


Low serum levels of C1 esterase inhibitor (and its substrate C4) are diagnostic of **hereditary angioedema**, an inherited autosomal dominant condition that causes episodes of painless, non-pitting, well-circumscribed edema. The face, neck, lips, and tongue are most commonly affected, but internal organs may also be involved. Angioedema affecting the tracheobronchial tree can cause respiratory obstruction and is potentially fatal. Angioedema of the gastrointestinal tract manifests with abdominal pain, vomiting, and diarrhea.

Normally, **C1 esterase inhibitor** suppresses activation of the C1 complement component and therefore the rest of the classic complement pathway. It also inactivates **kallikrein**, which catalyzes the conversion of kininogen to bradykinin. In **hereditary** angioedema, low C1 esterase inhibitor activity leads to an increase in active kallikrein and bradykinin levels. **Bradykinin** (along with C3a and C5a) mediate angioedema by increasing vasodilation and vascular permeability.

Angioedema may also occur as a side effect of **angiotensin-converting enzyme (ACE) inhibitor** medications. ACE normally catalyzes the conversion of angiotensin I into angiotensin II. ACE also converts bradykinin into inactive metabolites. ACE inhibitors can therefore lead to **bradykinin accumulation**. These medications should **not** be used in patients with hereditary angioedema as they may precipitate disease episodes.

(Choice B) Furosemide can cause hypokalemia, hyperuricemia, and hypovolemia. Ototoxicity may occur if furosemide is used with aminoglycosides.

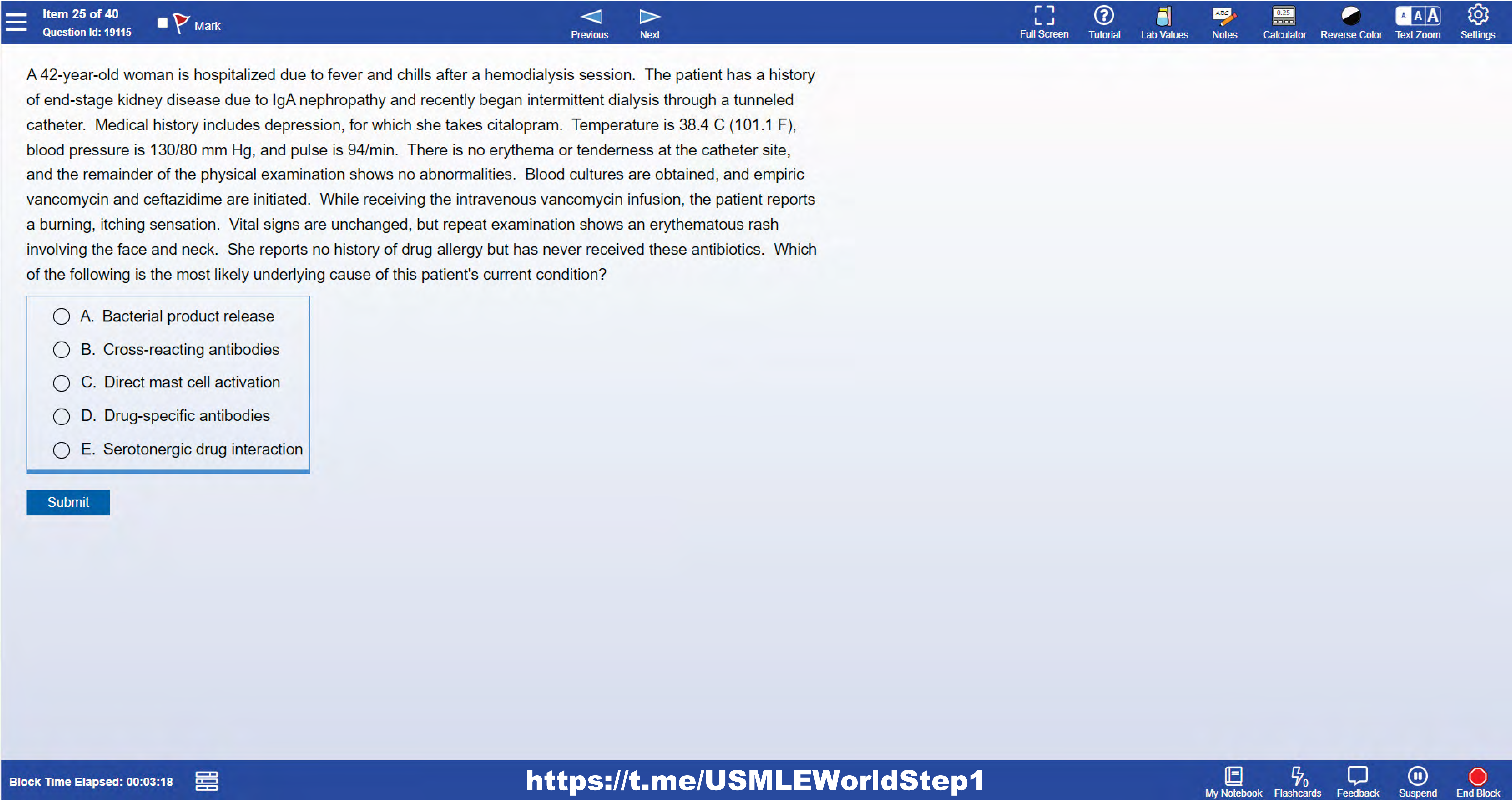
(Choice C) Methotrexate can cause hepatitis, pulmonary fibrosis, and bone marrow suppression.

(Choice D) Metoprolol is a selective β1-adrenergic blocker with few side effects. It may cause heart block in patients with conduction system disease and bronchoconstriction in asthmatic patients (rare due to β1 selectivity but can still occur).

(Choice E) The most common side effect of penicillin is hypersensitivity.

Educational objective:

Angioedema can be hereditary (autosomal dominant) or acquired (associated with angiotensin-converting enzyme [ACE] inhibitor treatment). In hereditary angioedema, low C1 esterase inhibitor activity leads to increases in bradykinin activity. ACE inhibitors should not be used in these patients.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A 42-year-old woman is hospitalized due to fever and chills after a hemodialysis session. The patient has a history of end-stage kidney disease due to IgA nephropathy and recently began intermittent dialysis through a tunneled catheter. Medical history includes depression, for which she takes citalopram. Temperature is 38.4 C (101.1 F), blood pressure is 130/80 mm Hg, and pulse is 94/min. There is no erythema or tenderness at the catheter site, and the remainder of the physical examination shows no abnormalities. Blood cultures are obtained, and empiric vancomycin and ceftazidime are initiated. While receiving the intravenous vancomycin infusion, the patient reports a burning, itching sensation. Vital signs are unchanged, but repeat examination shows an erythematous rash involving the face and neck. She reports no history of drug allergy but has never received these antibiotics. Which of the following is the most likely underlying cause of this patient's current condition?

○ A. Bacterial product release
○ B. Cross-reacting antibodies
○ C. Direct mast cell activation
○ D. Drug-specific antibodies
○ E. Serotonergic drug interaction

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✗ ● A. Bacterial product release (2%)

○ B. Cross-reacting antibodies (5%)

✓ ○ C. Direct mast cell activation (85%)

○ D. Drug-specific antibodies (3%)

○ E. Serotonergic drug interaction (3%)

Incorrect
Correct answer
C

85%
Answered correctly

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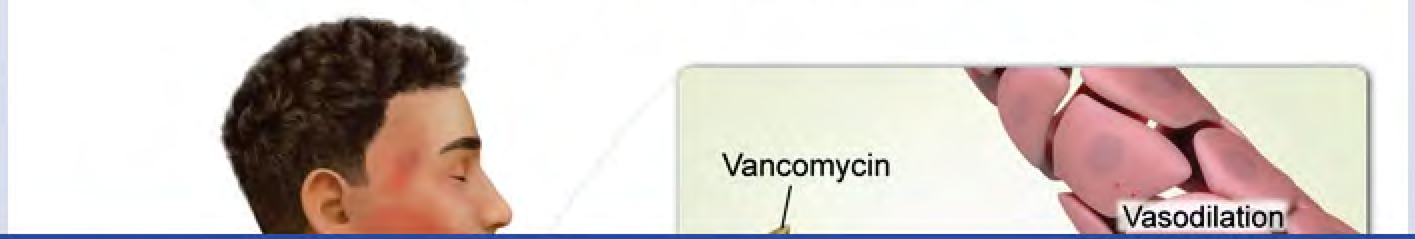
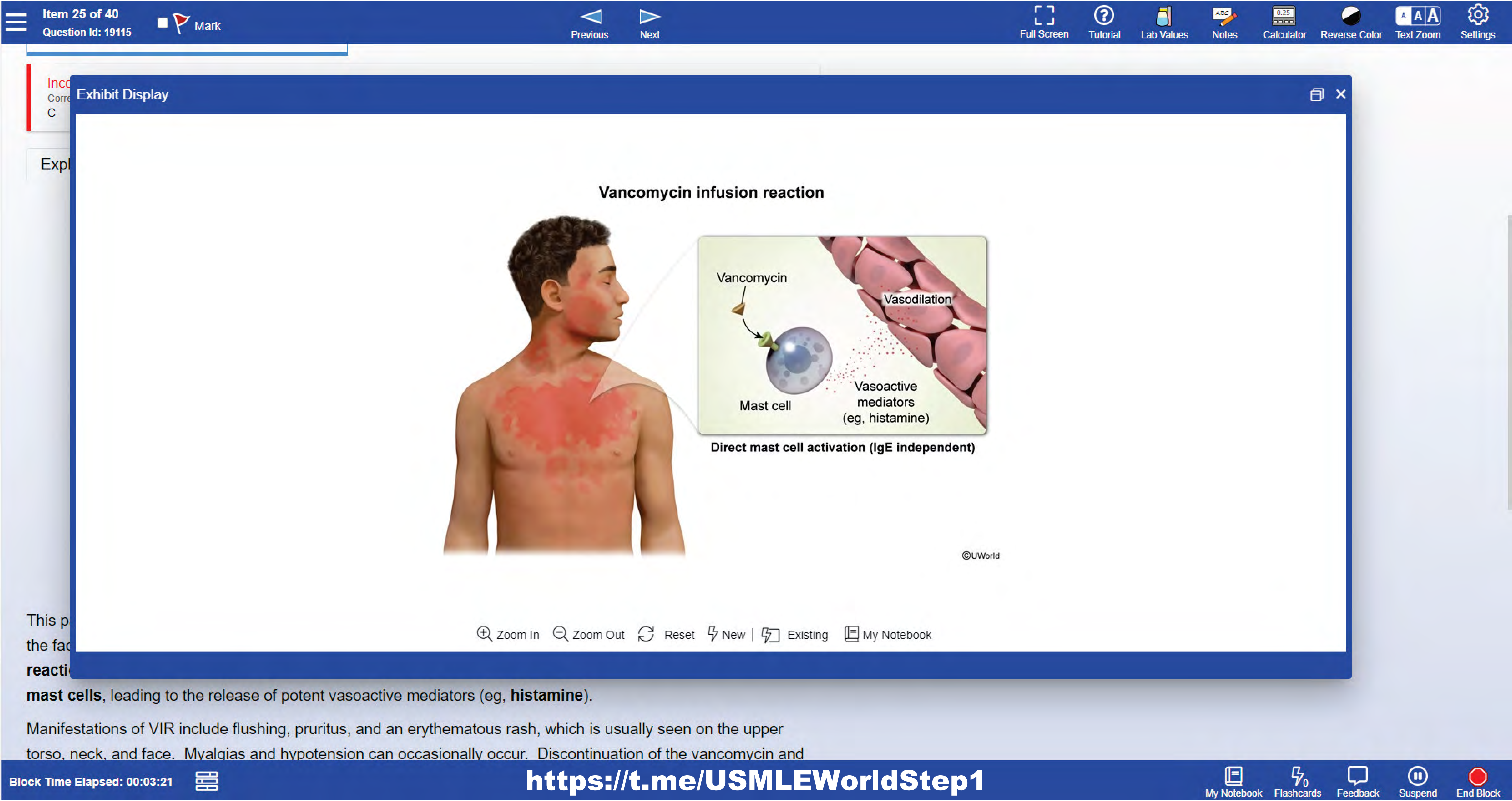
Explanation

Vancomycin infusion reaction

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Vancomycin infusion reaction
Vancomycin
Vasodilation
Mast cell
Vasoactive mediators (eg, histamine)
Direct mast cell activation (IgE independent)
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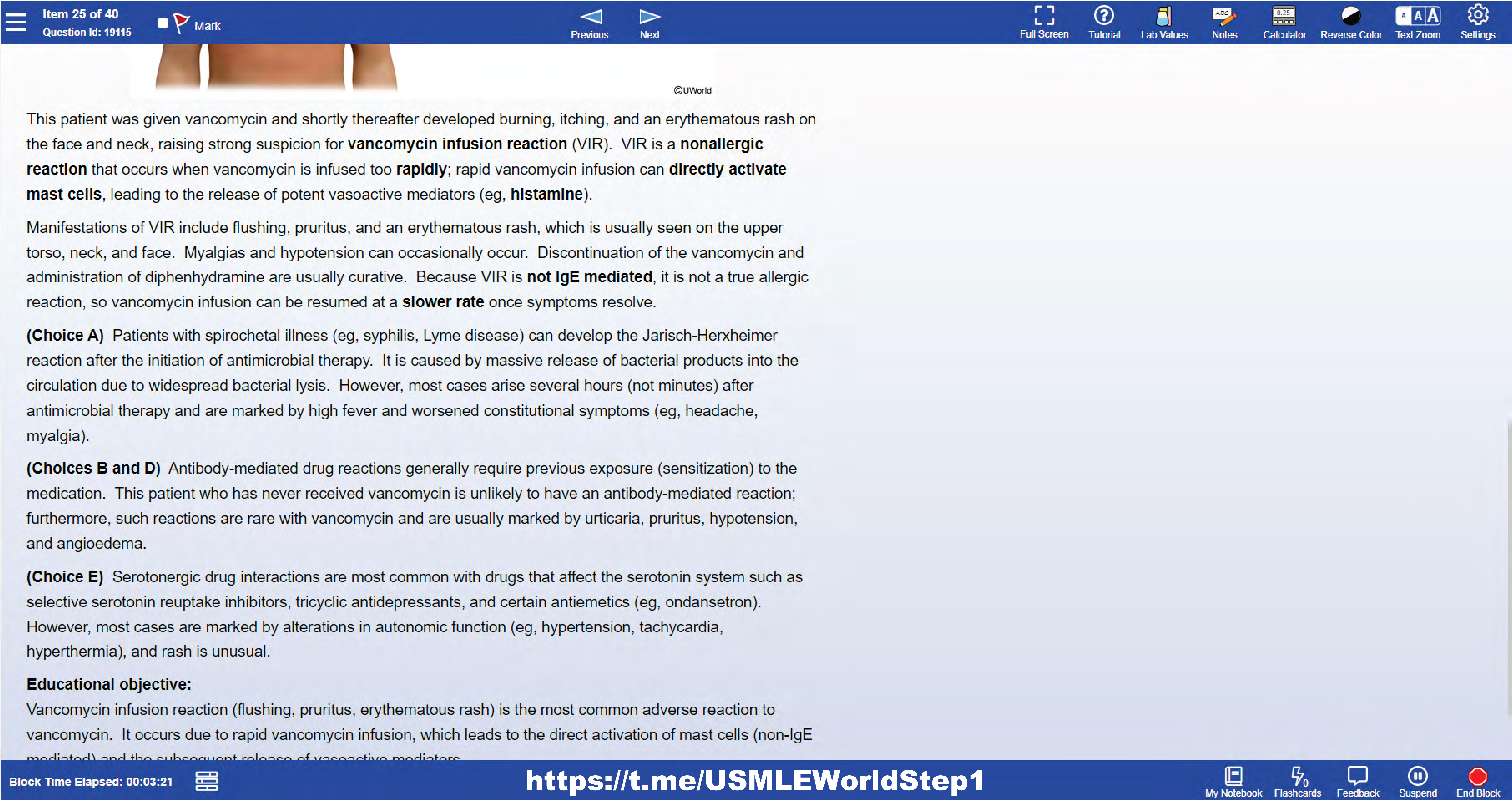
mast cells, leading to the release of potent vasoactive mediators (eg, **histamine**).

Manifestations of VIR include flushing, pruritus, and an erythematous rash, which is usually seen on the upper torso, neck, and face. Myalgias and hypotension can occasionally occur. Discontinuation of the vancomycin and



This patient was given vancomycin and shortly thereafter developed burning, itching, and an erythematous rash on the face and neck, raising strong suspicion for **vancomycin infusion reaction** (VIR). VIR is a **nonallergic reaction** that occurs when vancomycin is infused too **rapidly**; rapid vancomycin infusion can **directly activate mast cells**, leading to the release of potent vasoactive mediators (eg, **histamine**).

Manifestations of VIR include flushing, pruritus, and an erythematous rash, which is usually seen on the upper torso, neck, and face. Myalgias and hypotension can occasionally occur. Discontinuation of the vancomycin and administration of diphenhydramine are usually curative. Because VIR is **not IgE mediated**, it is not a true allergic reaction, so vancomycin infusion can be resumed at a **slower rate** once symptoms resolve.

(Choice A) Patients with spirochetal illness (eg, syphilis, Lyme disease) can develop the Jarisch-Herxheimer reaction after the initiation of antimicrobial therapy. It is caused by massive release of bacterial products into the circulation due to widespread bacterial lysis. However, most cases arise several hours (not minutes) after antimicrobial therapy and are marked by high fever and worsened constitutional symptoms (eg, headache, myalgia).

(Choices B and D) Antibody-mediated drug reactions generally require previous exposure (sensitization) to the medication. This patient who has never received vancomycin is unlikely to have an antibody-mediated reaction; furthermore, such reactions are rare with vancomycin and are usually marked by urticaria, pruritus, hypotension, and angioedema.

(Choice E) Serotonergic drug interactions are most common with drugs that affect the serotonin system such as selective serotonin reuptake inhibitors, tricyclic antidepressants, and certain antiemetics (eg, ondansetron). However, most cases are marked by alterations in autonomic function (eg, hypertension, tachycardia, hyperthermia), and rash is unusual.

Educational objective:

Vancomycin infusion reaction (flushing, pruritus, erythematous rash) is the most common adverse reaction to vancomycin. It occurs due to rapid vancomycin infusion, which leads to the direct activation of mast cells (non-IgE mediated) and the subsequent release of vasoactive mediators.

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the face and neck, raising strong suspicion for **vancomycin infusion reaction** (VIR). VIR is a **nonallergic reaction** that occurs when vancomycin is infused too **rapidly**; rapid vancomycin infusion can **directly activate mast cells**, leading to the release of potent vasoactive mediators (eg, **histamine**).

Manifestations of VIR include flushing, pruritus, and an erythematous rash, which is usually seen on the upper torso, neck, and face. Myalgias and hypotension can occasionally occur. Discontinuation of the vancomycin and administration of diphenhydramine are usually curative. Because VIR is **not IgE mediated**, it is not a true allergic reaction, so vancomycin infusion can be resumed at a **slower rate** once symptoms resolve.

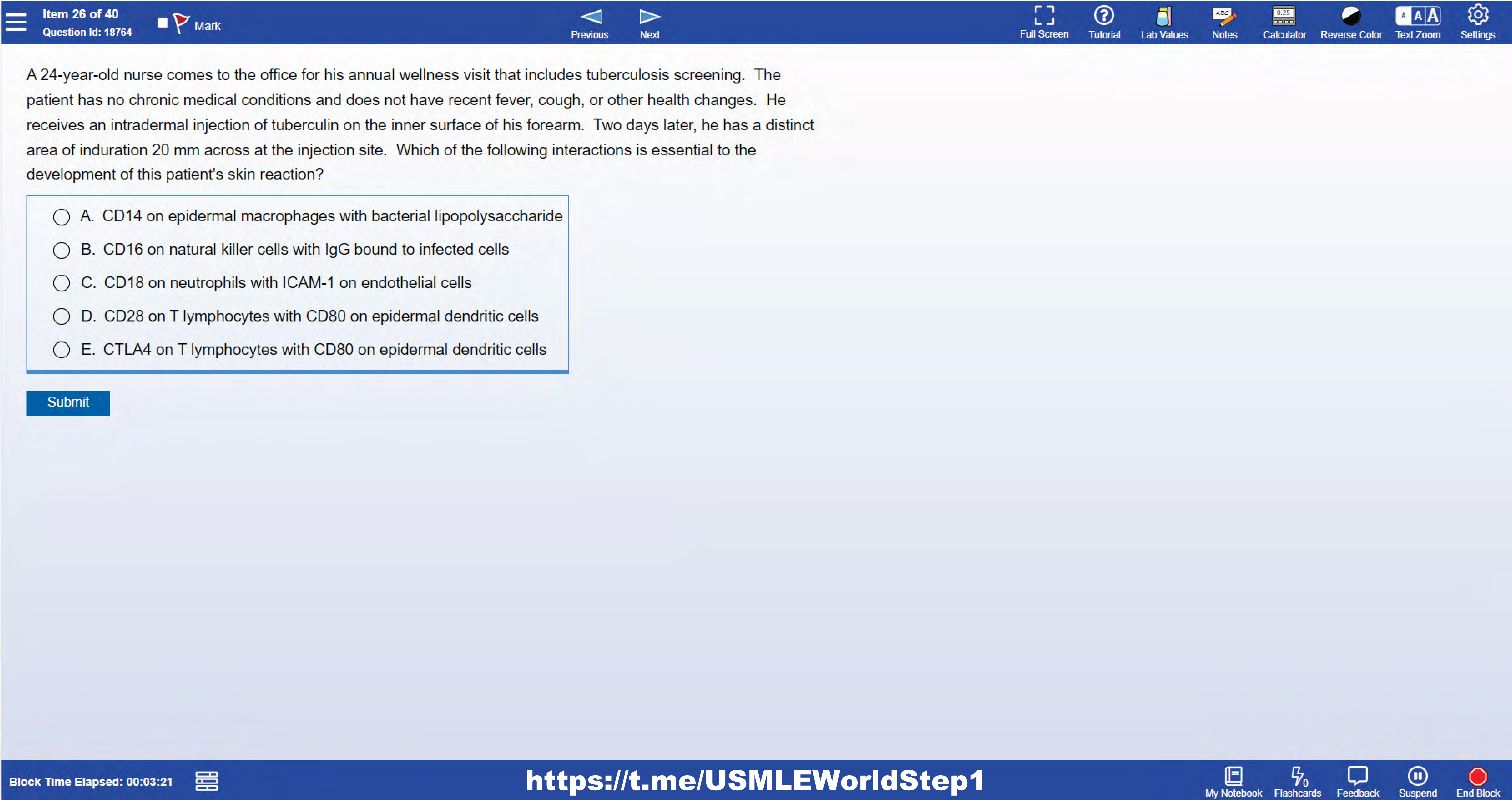
(Choice A) Patients with spirochetal illness (eg, syphilis, Lyme disease) can develop the Jarisch-Herxheimer reaction after the initiation of antimicrobial therapy. It is caused by massive release of bacterial products into the circulation due to widespread bacterial lysis. However, most cases arise several hours (not minutes) after antimicrobial therapy and are marked by high fever and worsened constitutional symptoms (eg, headache, myalgia).

(Choices B and D) Antibody-mediated drug reactions generally require previous exposure (sensitization) to the medication. This patient who has never received vancomycin is unlikely to have an antibody-mediated reaction; furthermore, such reactions are rare with vancomycin and are usually marked by urticaria, pruritus, hypotension, and angioedema.

(Choice E) Serotonergic drug interactions are most common with drugs that affect the serotonin system such as selective serotonin reuptake inhibitors, tricyclic antidepressants, and certain antiemetics (eg, ondansetron). However, most cases are marked by alterations in autonomic function (eg, hypertension, tachycardia, hyperthermia), and rash is unusual.

Educational objective:
Vancomycin infusion reaction (flushing, pruritus, erythematous rash) is the most common adverse reaction to vancomycin. It occurs due to rapid vancomycin infusion, which leads to the direct activation of mast cells (non-IgE mediated) and the subsequent release of vasoactive mediators.

Pharmacology	Allergy & Immunology	Drug allergy
Subject	System	Topic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A 24-year-old nurse comes to the office for his annual wellness visit that includes tuberculosis screening. The patient has no chronic medical conditions and does not have recent fever, cough, or other health changes. He receives an intradermal injection of tuberculin on the inner surface of his forearm. Two days later, he has a distinct area of induration 20 mm across at the injection site. Which of the following interactions is essential to the development of this patient's skin reaction?

○ A. CD14 on epidermal macrophages with bacterial lipopolysaccharide
○ B. CD16 on natural killer cells with IgG bound to infected cells
○ C. CD18 on neutrophils with ICAM-1 on endothelial cells
○ D. CD28 on T lymphocytes with CD80 on epidermal dendritic cells
○ E. CTLA4 on T lymphocytes with CD80 on epidermal dendritic cells

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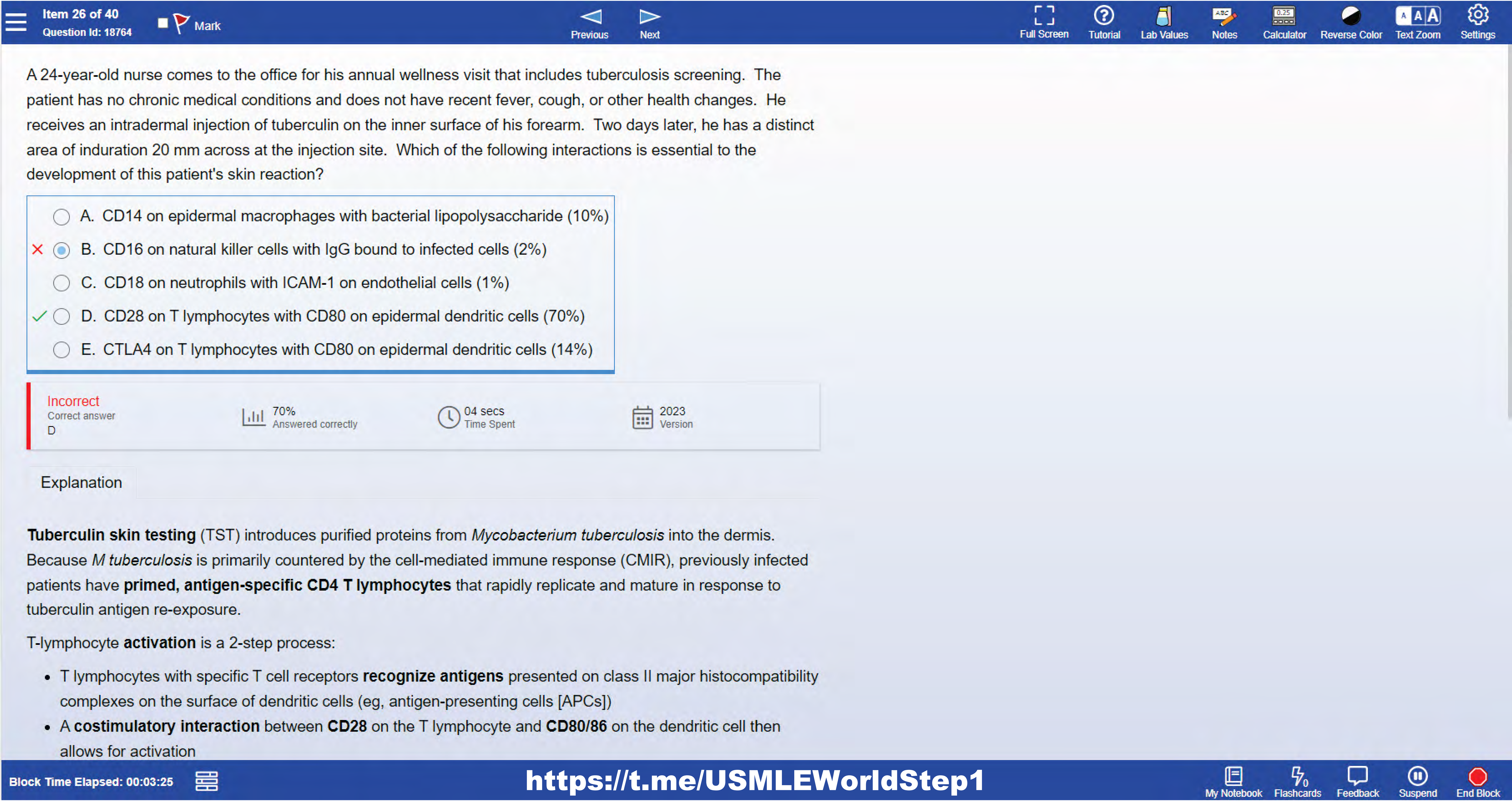
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- ○ A. CD14 on epidermal macrophages with bacterial lipopolysaccharide (10%)
- ✗ ● B. CD16 on natural killer cells with IgG bound to infected cells (2%)
- ○ C. CD18 on neutrophils with ICAM-1 on endothelial cells (1%)
- ✓ ○ D. CD28 on T lymphocytes with CD80 on epidermal dendritic cells (70%)
- ○ E. CTLA4 on T lymphocytes with CD80 on epidermal dendritic cells (14%)

Incorrect
Correct answer
D

70%
Answered correctly

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Explanation

Tuberculin skin testing (TST) introduces purified proteins from *Mycobacterium tuberculosis* into the dermis. Because *M tuberculosis* is primarily countered by the cell-mediated immune response (CMIR), previously infected patients have **primed, antigen-specific CD4 T lymphocytes** that rapidly replicate and mature in response to tuberculin antigen re-exposure.

T-lymphocyte **activation** is a 2-step process:

- T lymphocytes with specific T cell receptors **recognize antigens** presented on class II major histocompatibility complexes on the surface of dendritic cells (eg, antigen-presenting cells [APCs])
- A **costimulatory interaction** between **CD28** on the T lymphocyte and **CD80/86** on the dendritic cell then allows for activation

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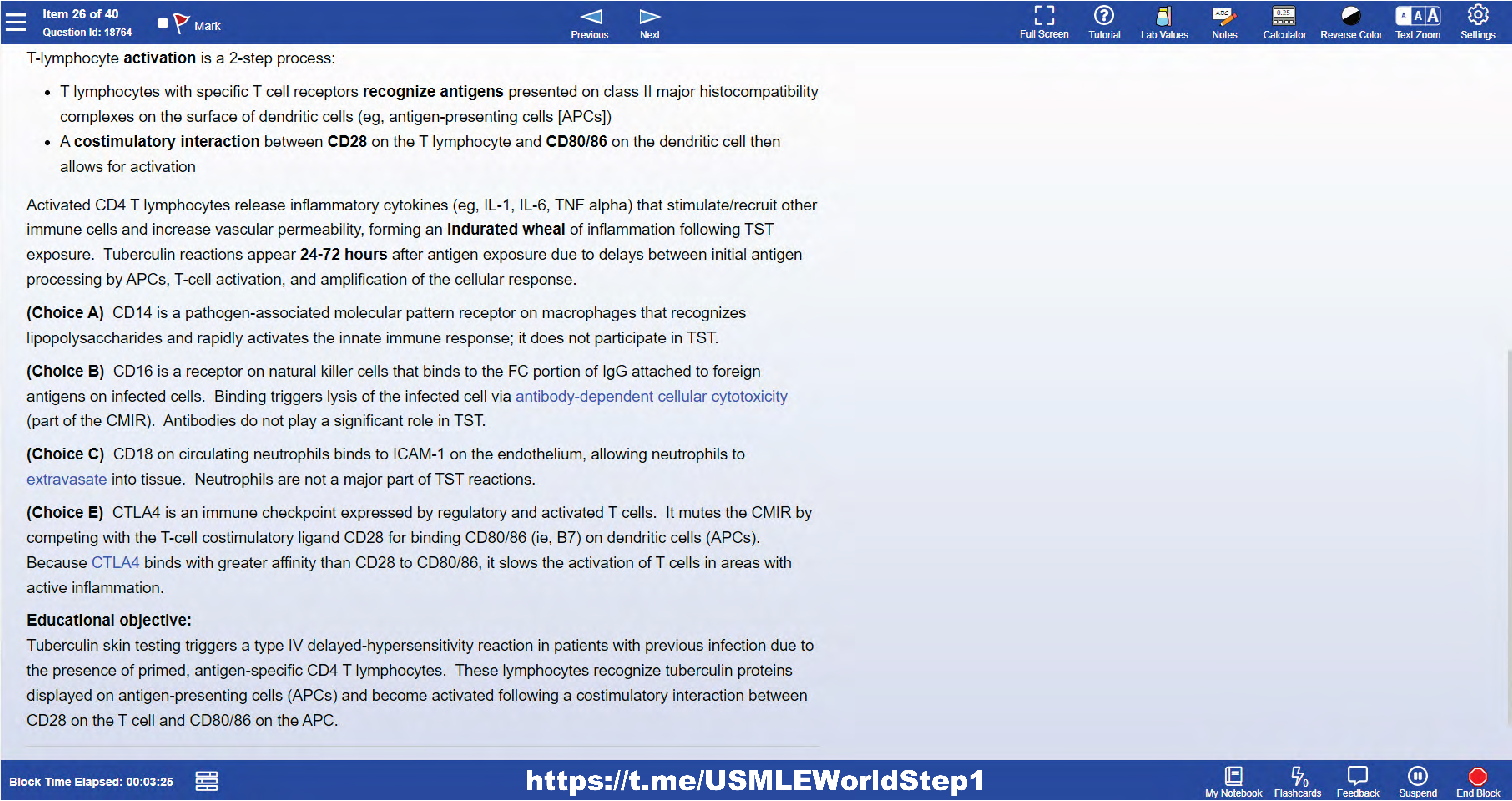
Activated CD4 T lymphocytes release inflammatory cytokines (eg, IL-1, IL-6, TNF alpha) that stimulate/recruit other immune cells and increase vascular permeability, forming an **indurated wheal** of inflammation following TST exposure. Tuberculin reactions appear **24-72 hours** after antigen exposure due to delays between initial antigen processing by APCs, T-cell activation, and amplification of the cellular response.

(Choice A) CD14 is a pathogen-associated molecular pattern receptor on macrophages that recognizes lipopolysaccharides and rapidly activates the innate immune response; it does not participate in TST.

(Choice B) CD16 is a receptor on natural killer cells that binds to the FC portion of IgG attached to foreign antigens on infected cells. Binding triggers lysis of the infected cell via antibody-dependent cellular cytotoxicity (part of the CMIR). Antibodies do not play a significant role in TST.

(Choice C) CD18 on circulating neutrophils binds to ICAM-1 on the endothelium, allowing neutrophils to extravasate into tissue. Neutrophils are not a major part of TST reactions.

(Choice E) CTLA4 is an immune checkpoint expressed by regulatory and activated T cells. It mutes the CMIR by competing with the T-cell costimulatory ligand CD28 for binding CD80/86 (ie, B7) on dendritic cells (APCs). Because CTLA4 binds with greater affinity than CD28 to CD80/86, it slows the activation of T cells in areas with active inflammation.



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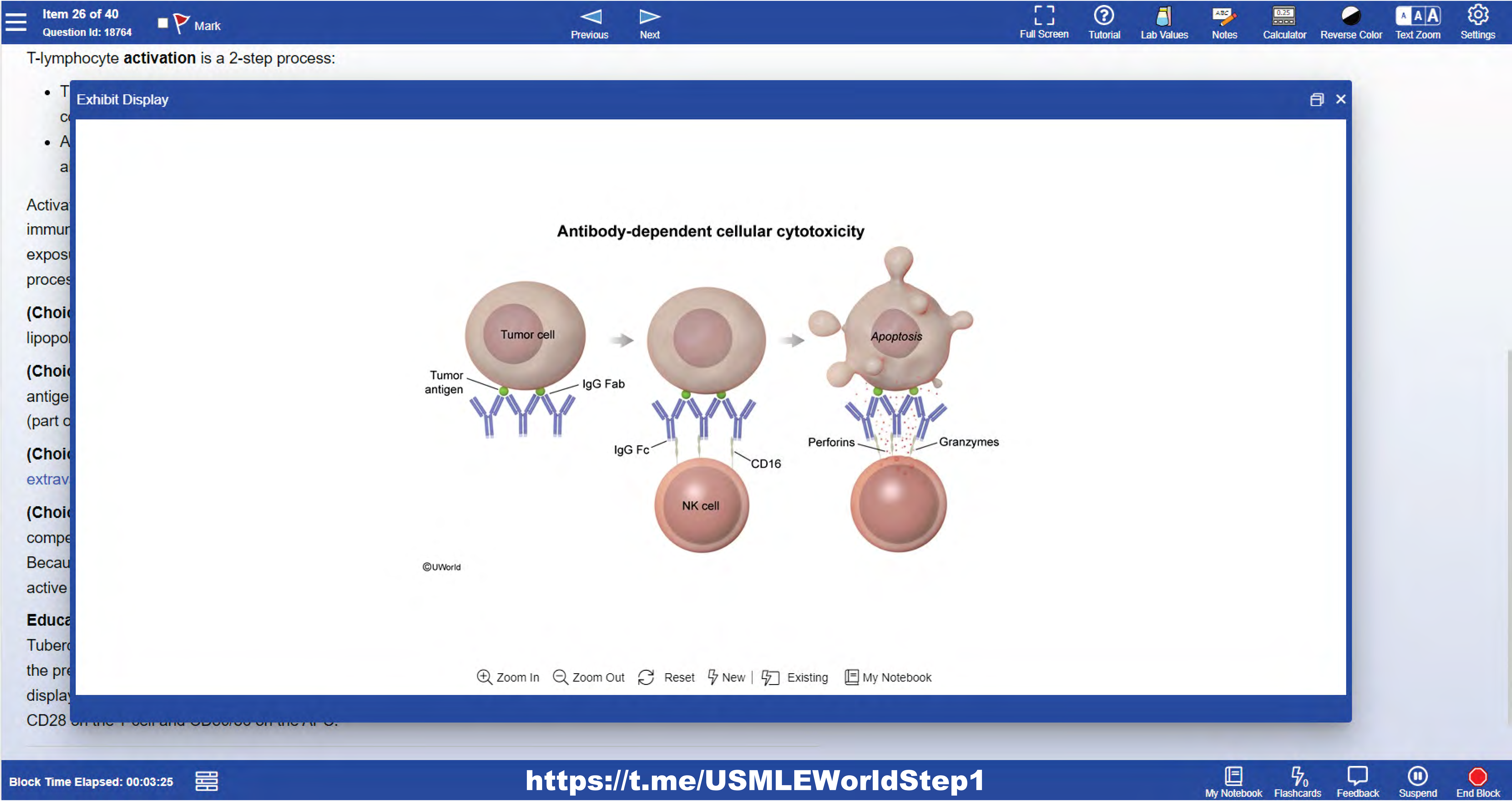
Educational objective:
Tuberculin skin testing triggers a type IV delayed-hypersensitivity reaction in patients with previous infection due to the presence of primed, antigen-specific CD4 T lymphocytes. These lymphocytes recognize tuberculin proteins displayed on antigen-presenting cells (APCs) and become activated following a costimulatory interaction between CD28 on the T cell and CD80/86 on the APC.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Antibody-dependent cellular cytotoxicity
Tumor cell
Tumor antigen
IgG Fab
IgG Fc
CD16
NK cell
Apoptosis
Perforins
Granzymes
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T-lymphocyte **activation** is a 2-step process:

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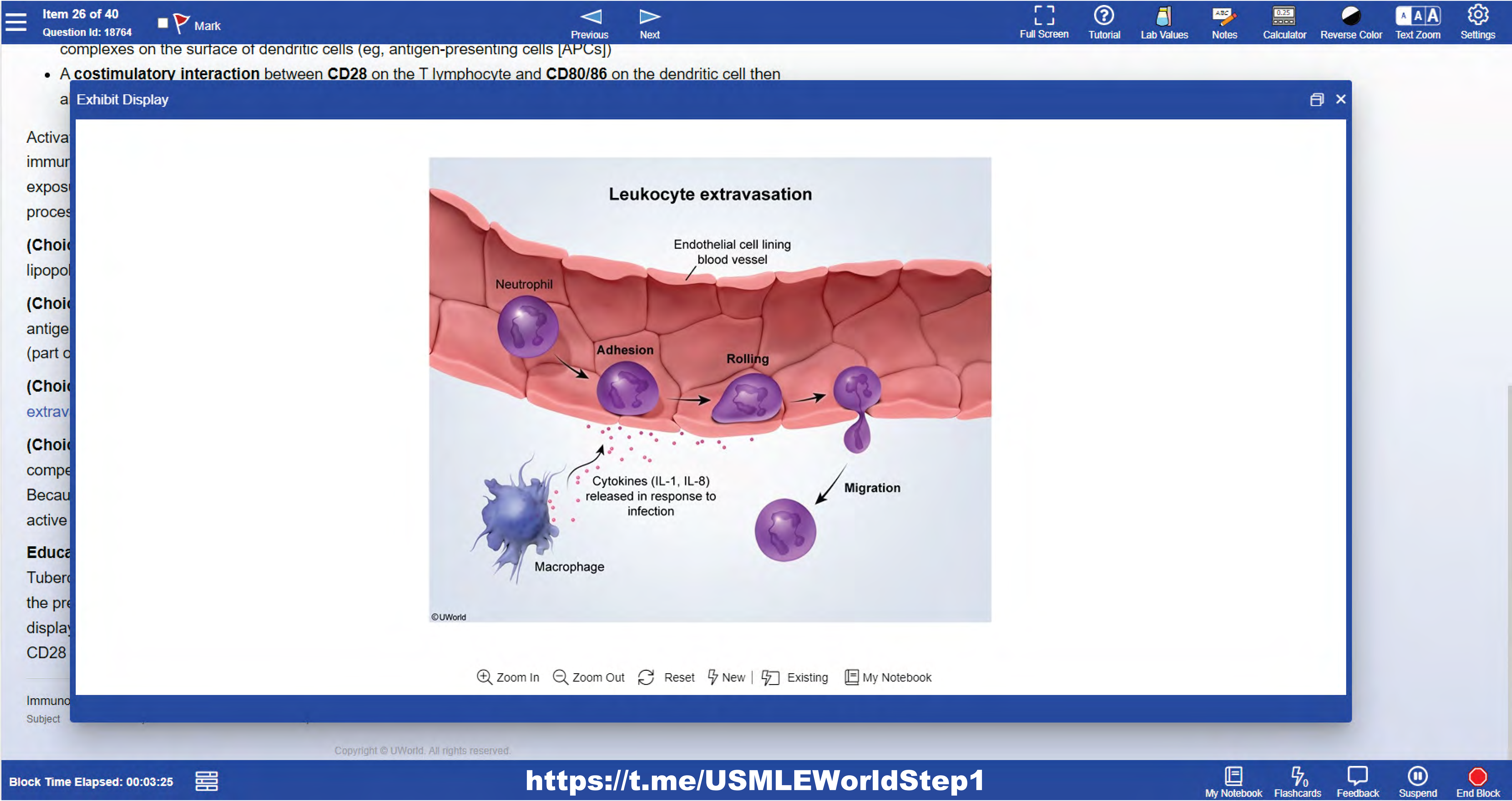
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Leukocyte extravasation

Endothelial cell lining blood vessel
Neutrophil
Adhesion
Rolling
Cytokines (IL-1, IL-8) released in response to infection
Migration
Macrophage
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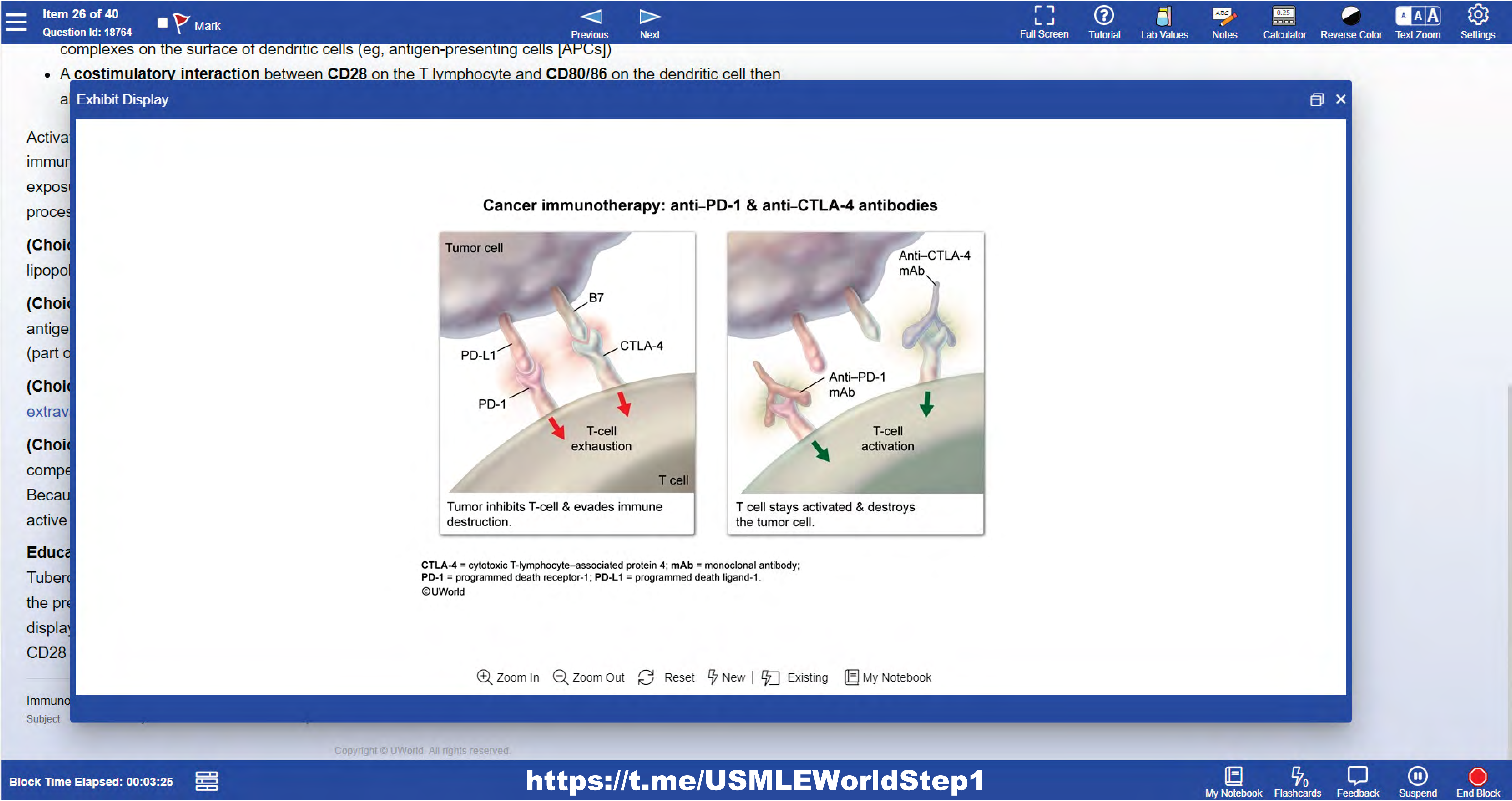
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Cancer immunotherapy: anti–PD-1 & anti–CTLA-4 antibodies

Tumor cell
B7
CTLA-4
PD-L1
PD-1
T-cell exhaustion
T cell
Anti–CTLA-4 mAb
Anti–PD-1 mAb
T-cell activation

Tumor inhibits T-cell & evades immune destruction.

T cell stays activated & destroys the tumor cell.

CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; **mAb** = monoclonal antibody;
PD-1 = programmed death receptor-1; **PD-L1** = programmed death ligand-1.
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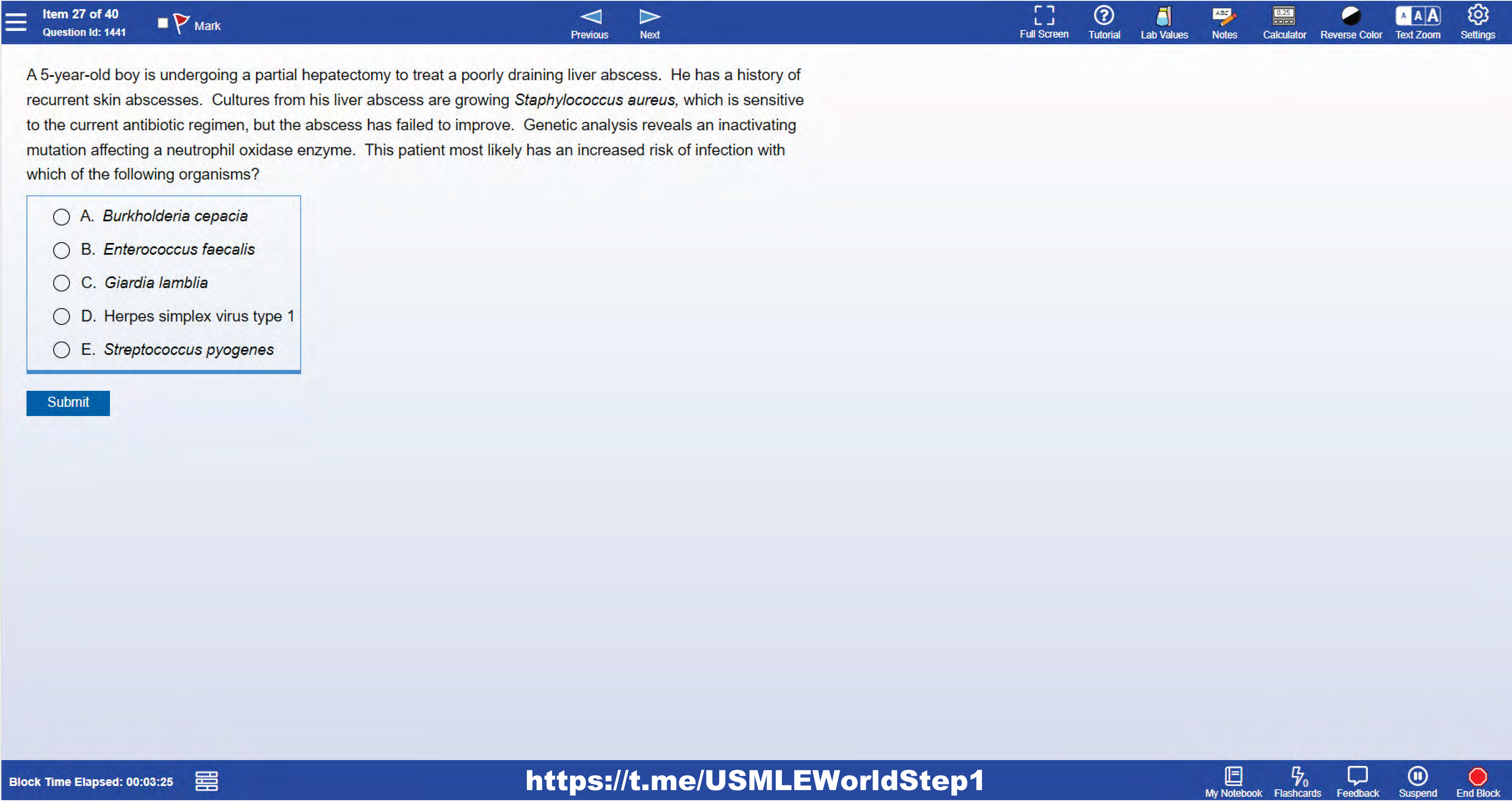
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A 5-year-old boy is undergoing a partial hepatectomy to treat a poorly draining liver abscess. He has a history of recurrent skin abscesses. Cultures from his liver abscess are growing *Staphylococcus aureus*, which is sensitive to the current antibiotic regimen, but the abscess has failed to improve. Genetic analysis reveals an inactivating mutation affecting a neutrophil oxidase enzyme. This patient most likely has an increased risk of infection with which of the following organisms?

- ○ A. *Burkholderia cepacia*
- ○ B. *Enterococcus faecalis*
- ○ C. *Giardia lamblia*
- ○ D. Herpes simplex virus type 1
- ○ E. *Streptococcus pyogenes*

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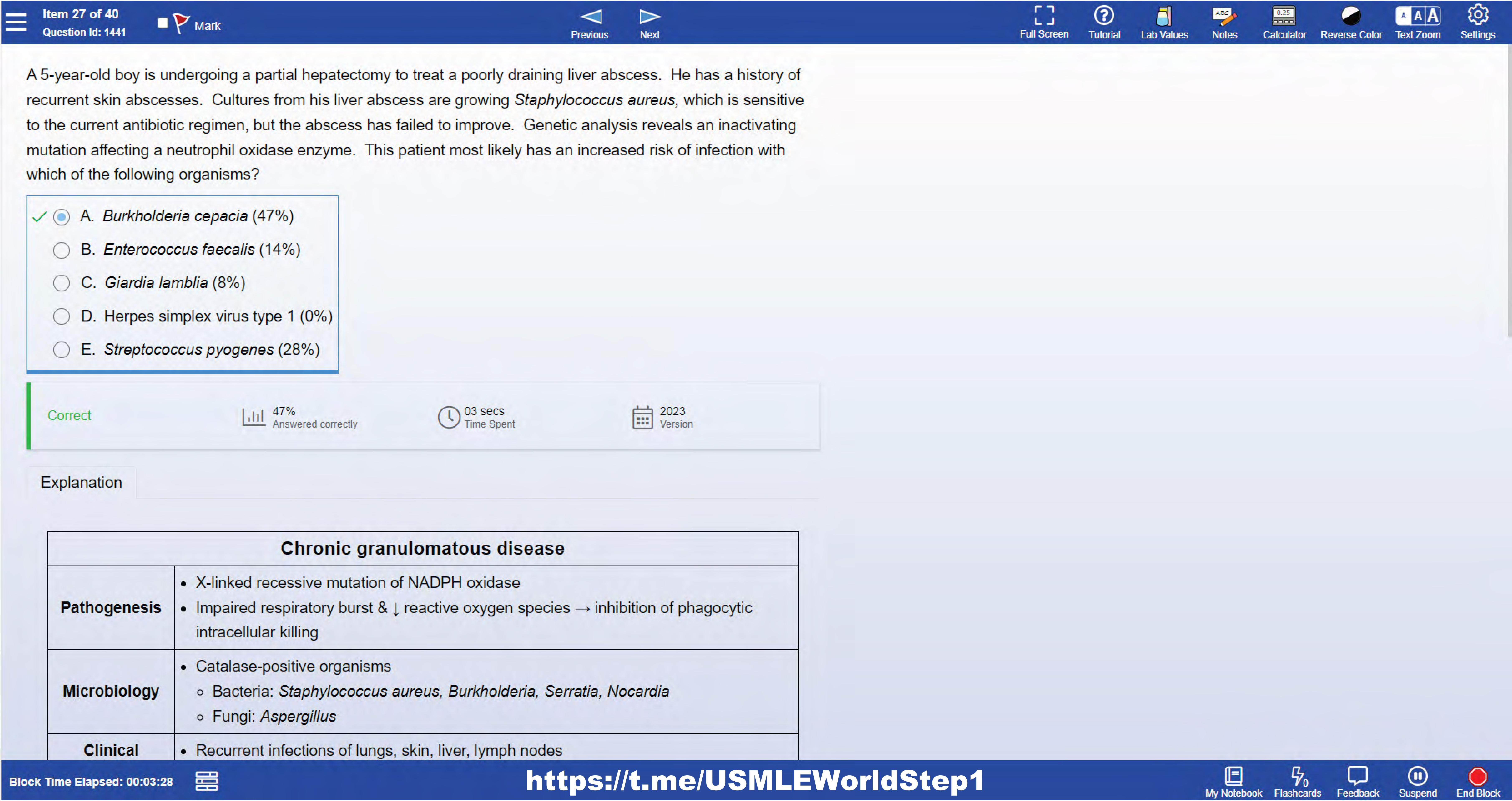
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✓ ● A. *Burkholderia cepacia* (47%)
○ B. *Enterococcus faecalis* (14%)
○ C. *Giardia lamblia* (8%)
○ D. Herpes simplex virus type 1 (0%)
○ E. *Streptococcus pyogenes* (28%)

Correct | 47% Answered correctly | 03 secs Time Spent | 2023 Version

Explanation

Chronic granulomatous disease	
Pathogenesis	• X-linked recessive mutation of NADPH oxidase • Impaired respiratory burst & ↓ reactive oxygen species → inhibition of phagocytic intracellular killing
Microbiology	• Catalase-positive organisms ◦ Bacteria: *Staphylococcus aureus, Burkholderia, Serratia, Nocardia* ◦ Fungi: *Aspergillus*
Clinical	• Recurrent infections of lungs, skin, liver, lymph nodes

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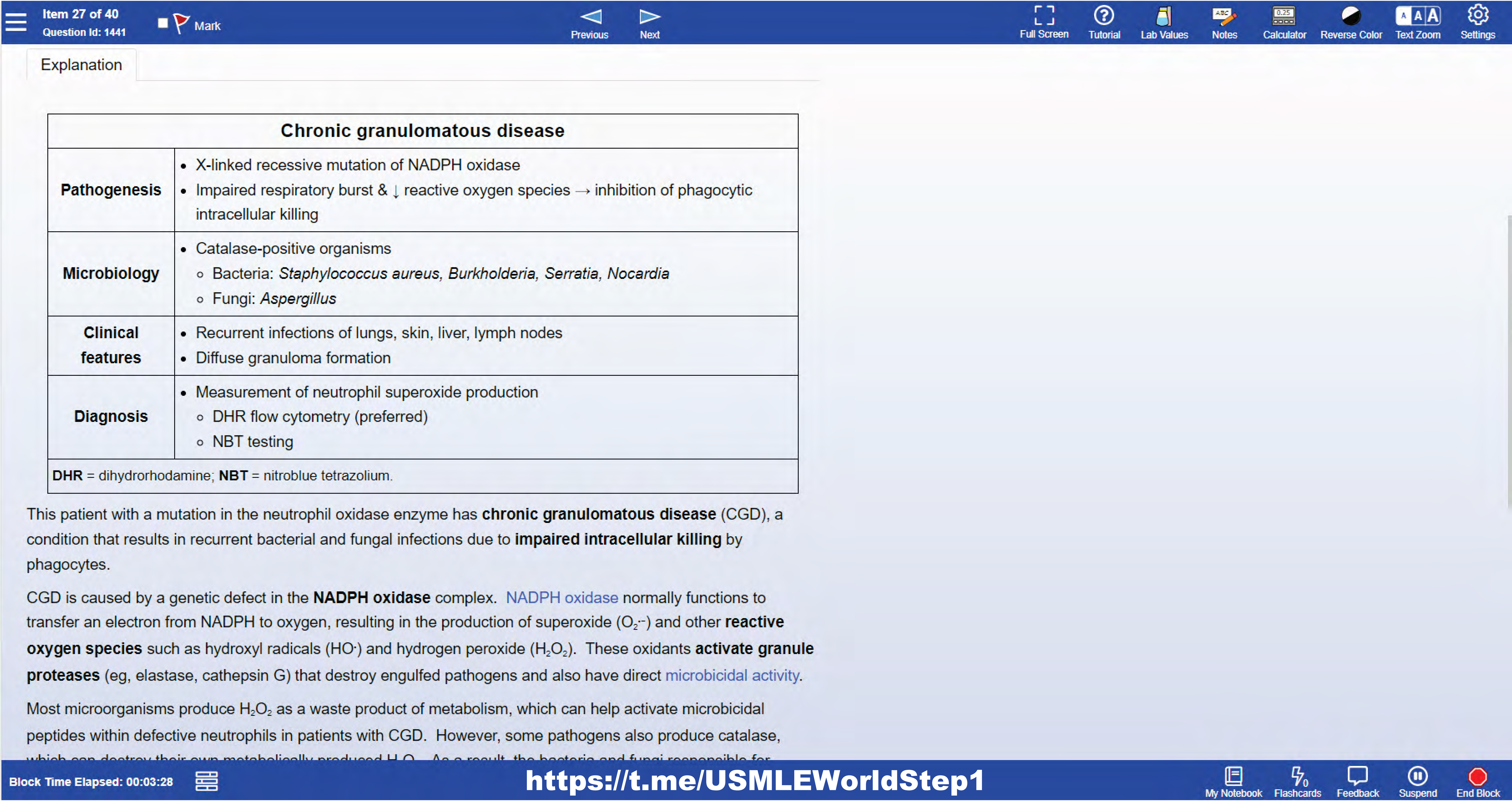
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Clinical features	• Recurrent infections of lungs, skin, liver, lymph nodes • Diffuse granuloma formation
Diagnosis	• Measurement of neutrophil superoxide production ◦ DHR flow cytometry (preferred) ◦ NBT testing

DHR = dihydrorhodamine; **NBT** = nitroblue tetrazolium.

This patient with a mutation in the neutrophil oxidase enzyme has **chronic granulomatous disease** (CGD), a condition that results in recurrent bacterial and fungal infections due to **impaired intracellular killing** by phagocytes.

CGD is caused by a genetic defect in the **NADPH oxidase** complex. NADPH oxidase normally functions to transfer an electron from NADPH to oxygen, resulting in the production of superoxide ($O_2^{\cdot -}$) and other **reactive oxygen species** such as hydroxyl radicals ($HO^{\cdot}$) and hydrogen peroxide (H_2O_2). These oxidants **activate granule proteases** (eg, elastase, cathepsin G) that destroy engulfed pathogens and also have direct microbicidal activity.

Most microorganisms produce H_2O_2 as a waste product of metabolism, which can help activate microbicidal peptides within defective neutrophils in patients with CGD. However, some pathogens also produce catalase,

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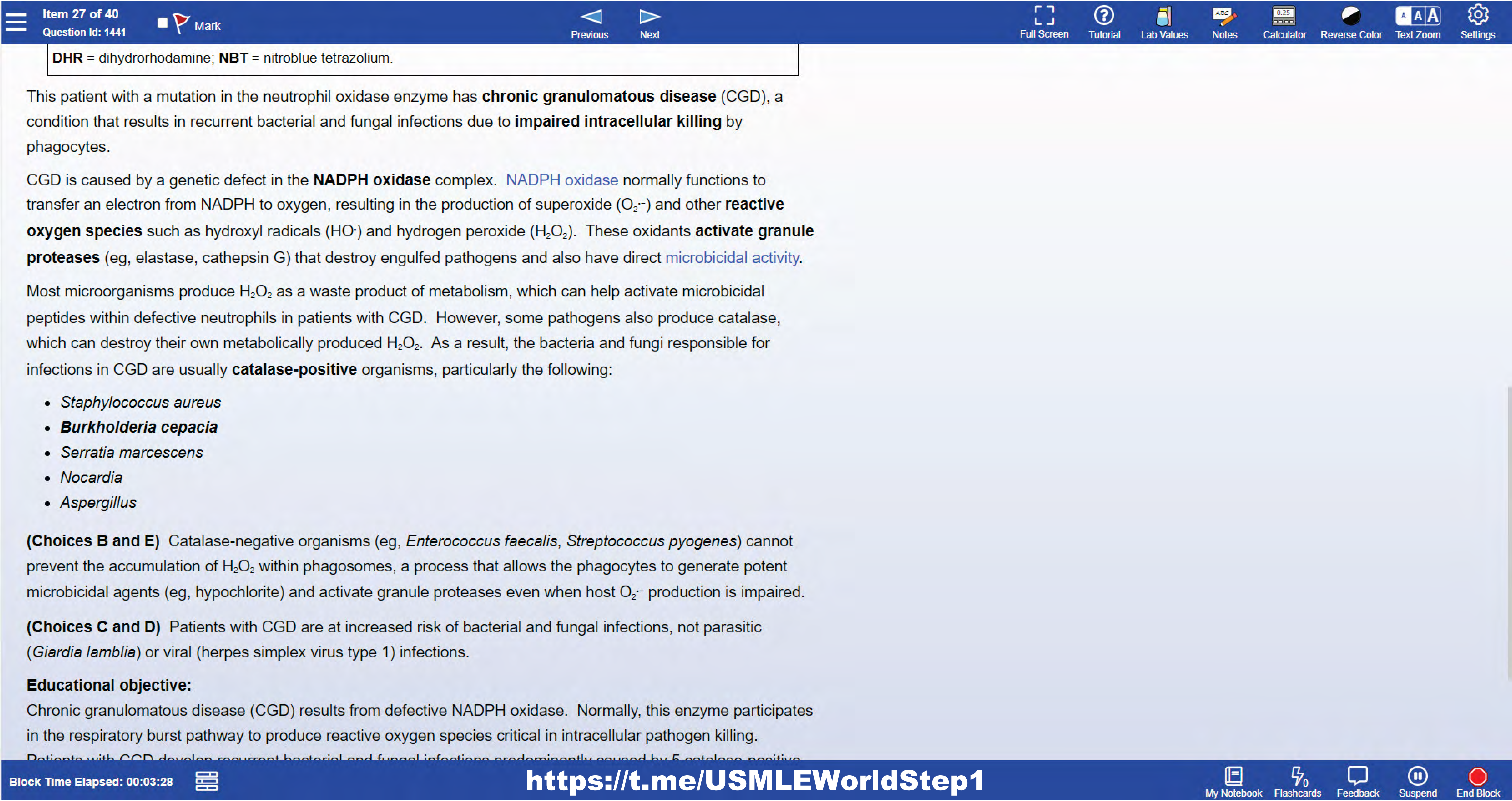

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Most microorganisms produce H_2O_2 as a waste product of metabolism, which can help activate microbicidal peptides within defective neutrophils in patients with CGD. However, some pathogens also produce catalase, which can destroy their own metabolically produced H_2O_2. As a result, the bacteria and fungi responsible for infections in CGD are usually **catalase-positive** organisms, particularly the following:

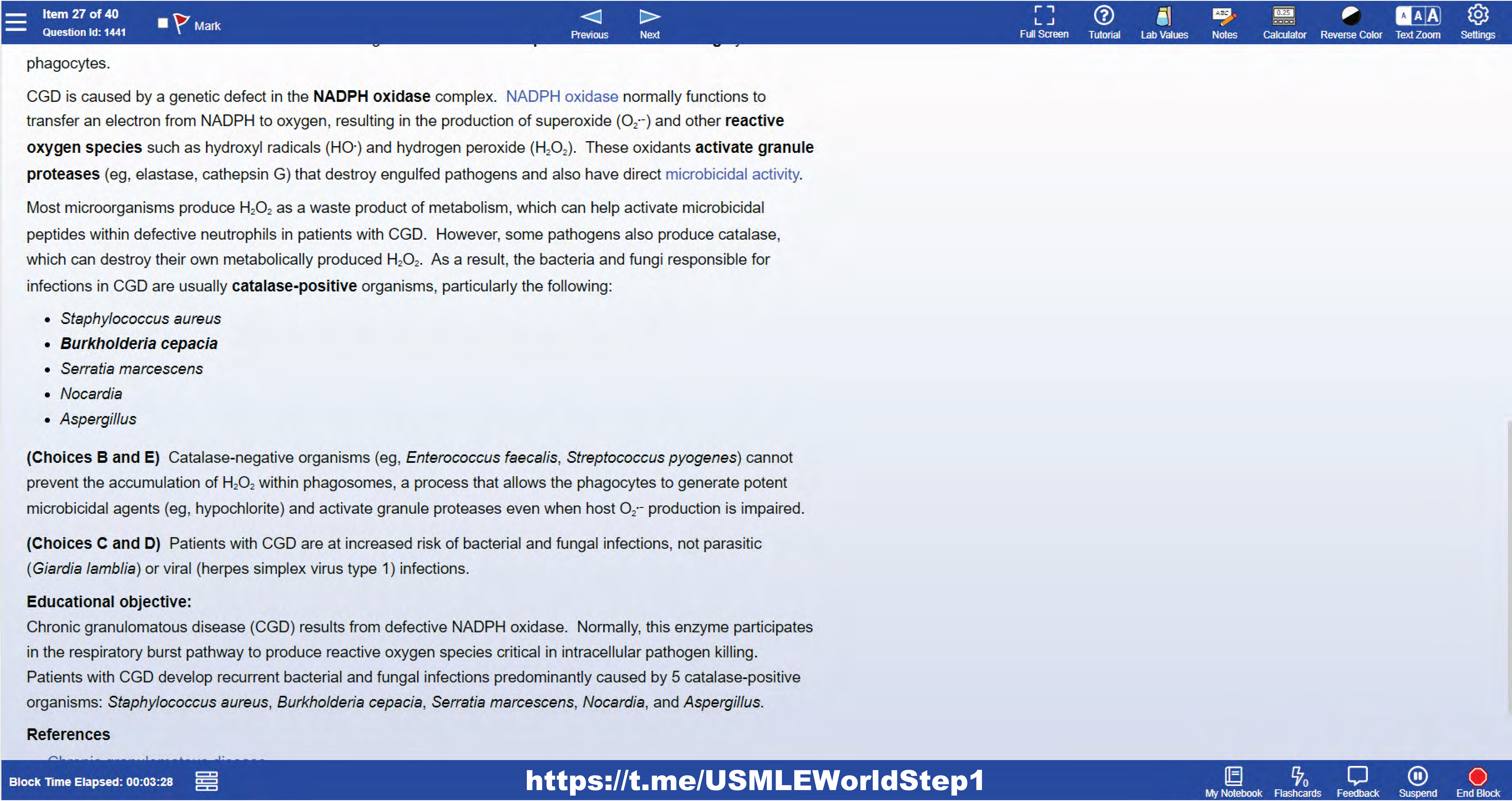
- *Staphylococcus aureus*
- ***Burkholderia cepacia***
- *Serratia marcescens*
- *Nocardia*
- *Aspergillus*

(Choices B and E) Catalase-negative organisms (eg, *Enterococcus faecalis*, *Streptococcus pyogenes*) cannot prevent the accumulation of H_2O_2 within phagosomes, a process that allows the phagocytes to generate potent microbicidal agents (eg, hypochlorite) and activate granule proteases even when host $O_2^{\cdot -}$ production is impaired.

(Choices C and D) Patients with CGD are at increased risk of bacterial and fungal infections, not parasitic (*Giardia lamblia*) or viral (herpes simplex virus type 1) infections.

Educational objective:

Chronic granulomatous disease (CGD) results from defective NADPH oxidase. Normally, this enzyme participates in the respiratory burst pathway to produce reactive oxygen species critical in intracellular pathogen killing. Patients with CGD develop recurrent bacterial and fungal infections predominantly caused by 5 catalase-positive



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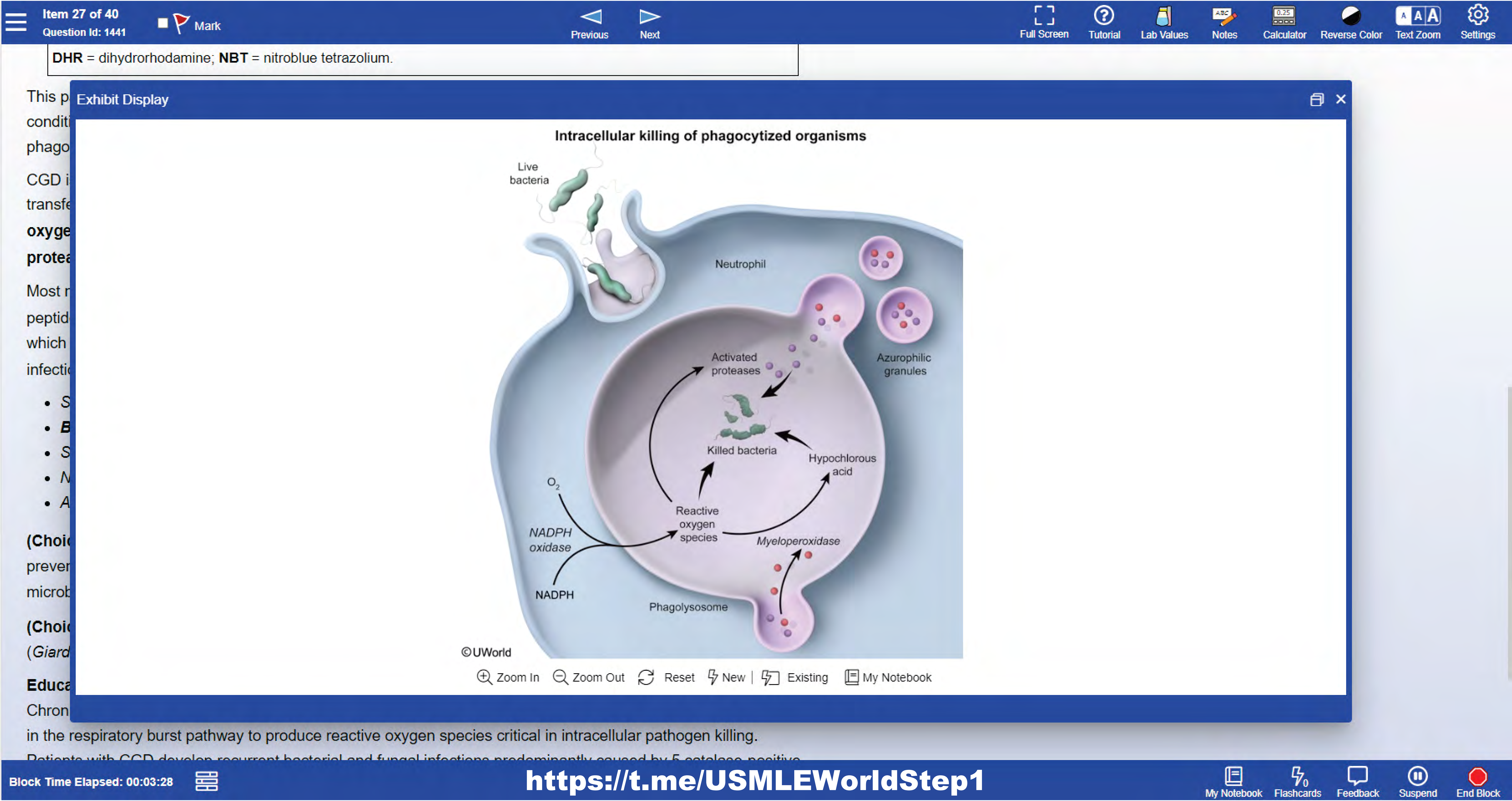
References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Live bacteria
Neutrophil
Azurophilic granules
Activated proteases
Killed bacteria
Hypochlorous acid
O2
Reactive oxygen species
NADPH oxidase
NADPH
Myeloperoxidase
Phagolysosome
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Intracellular killing of phagocytized organisms

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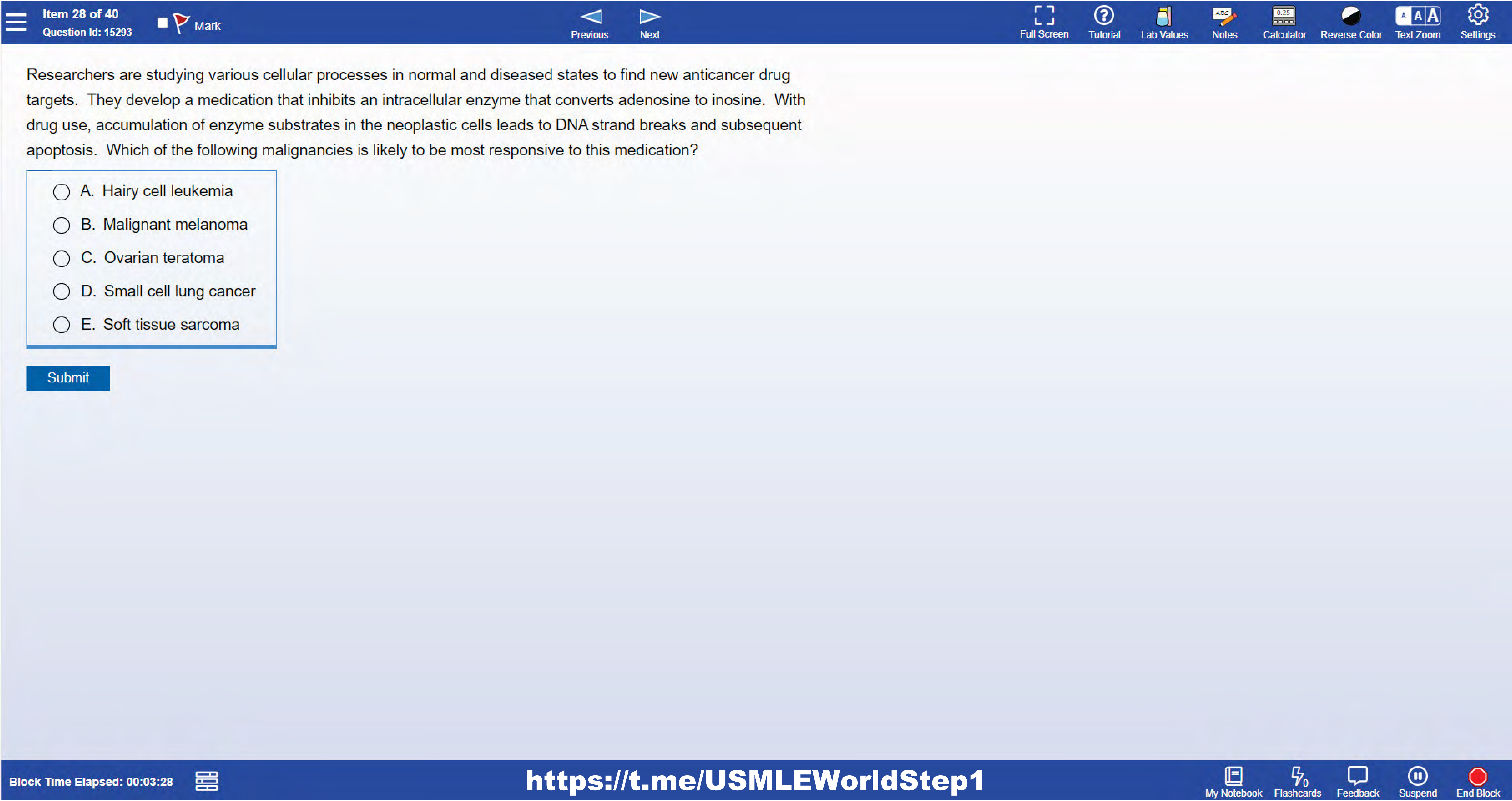
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Researchers are studying various cellular processes in normal and diseased states to find new anticancer drug targets. They develop a medication that inhibits an intracellular enzyme that converts adenosine to inosine. With drug use, accumulation of enzyme substrates in the neoplastic cells leads to DNA strand breaks and subsequent apoptosis. Which of the following malignancies is likely to be most responsive to this medication?

○ A. Hairy cell leukemia
○ B. Malignant melanoma
○ C. Ovarian teratoma
○ D. Small cell lung cancer
○ E. Soft tissue sarcoma

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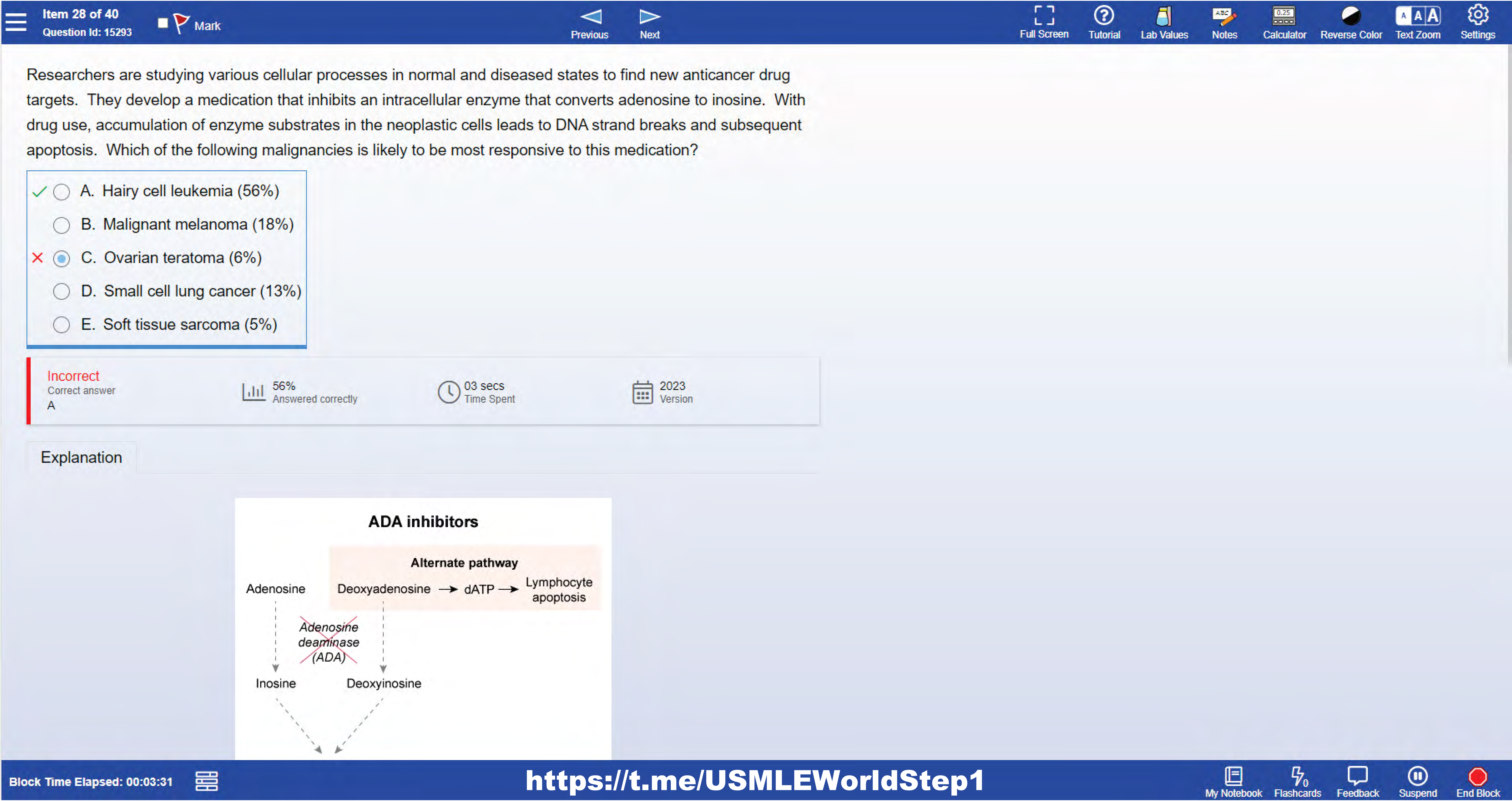
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✓ ○ A. Hairy cell leukemia (56%)
○ B. Malignant melanoma (18%)
✗ ● C. Ovarian teratoma (6%)
○ D. Small cell lung cancer (13%)
○ E. Soft tissue sarcoma (5%)

Incorrect
Correct answer
A

56%
Answered correctly

03 secs
Time Spent

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Explanation

ADA inhibitors

Alternate pathway
Adenosine
Deoxyadenosine
dATP
Lymphocyte apoptosis
~~Adenosine deaminase (ADA)~~
Inosine
Deoxyinosine

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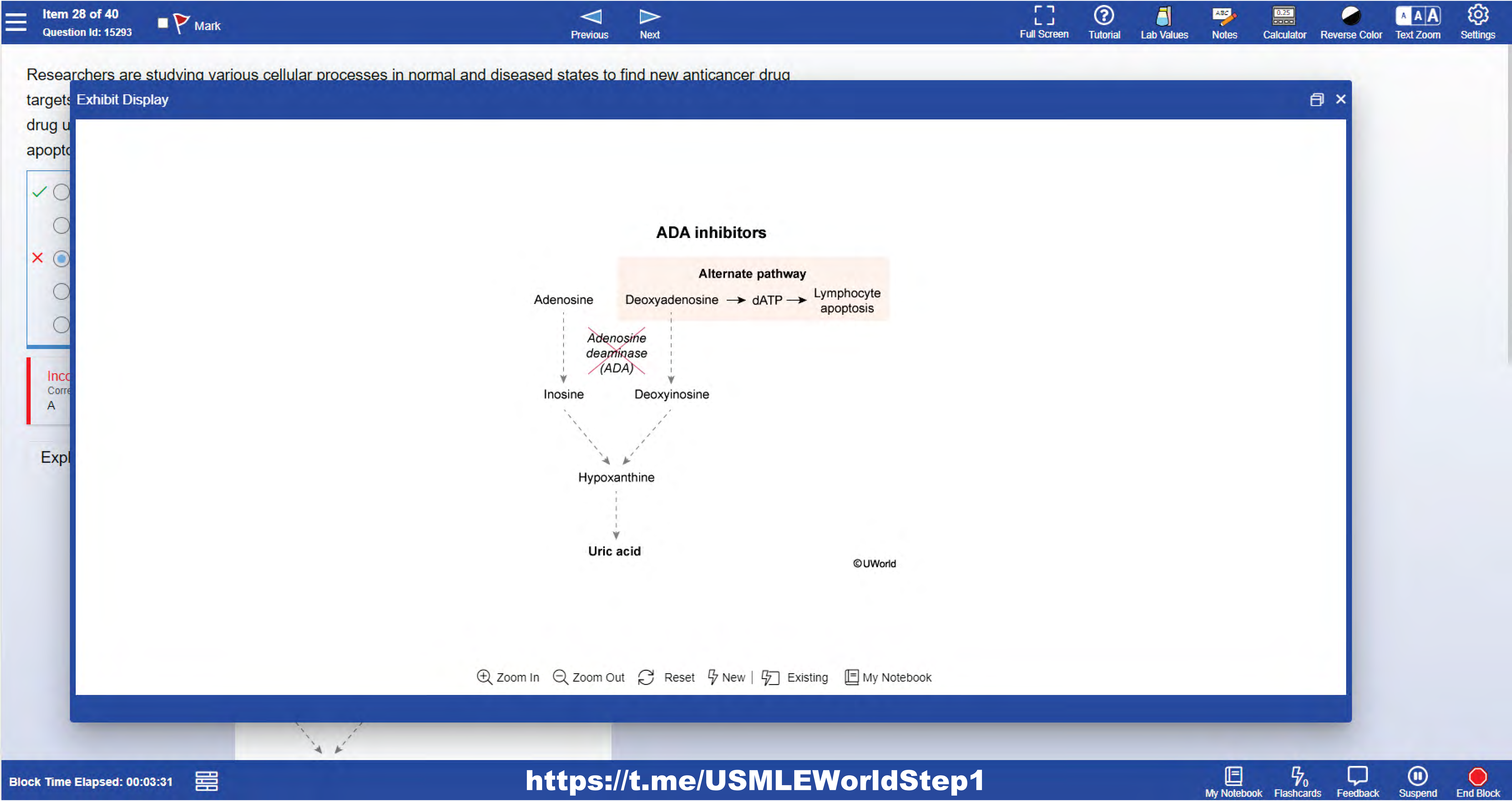
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ADA inhibitors

Alternate pathway
Adenosine
Deoxyadenosine → dATP → Lymphocyte apoptosis
~~Adenosine deaminase (ADA)~~
Inosine
Deoxyinosine
Hypoxanthine
Uric acid

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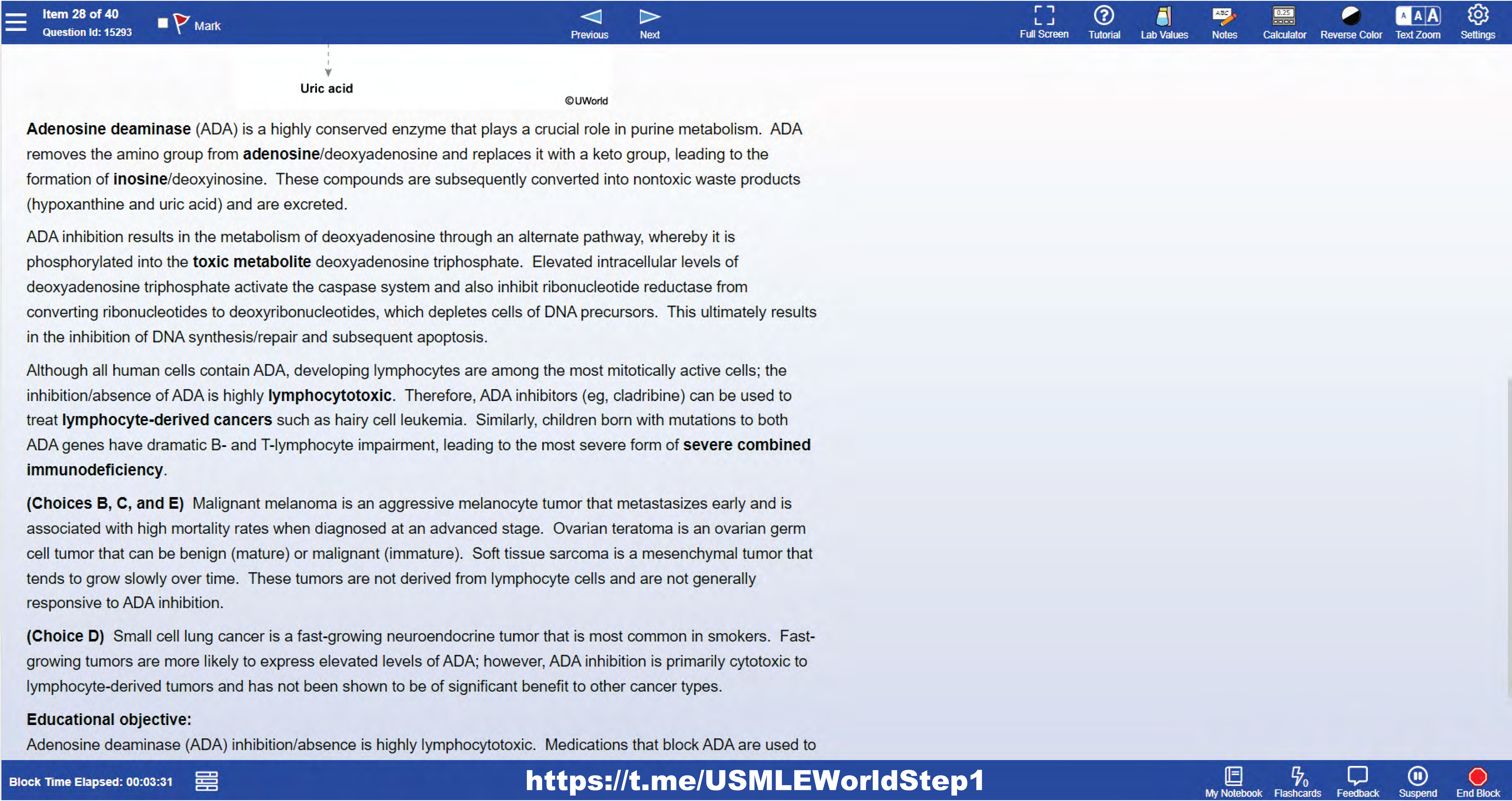


Adenosine deaminase (ADA) is a highly conserved enzyme that plays a crucial role in purine metabolism. ADA removes the amino group from **adenosine**/deoxyadenosine and replaces it with a keto group, leading to the formation of **inosine**/deoxyinosine. These compounds are subsequently converted into nontoxic waste products (hypoxanthine and uric acid) and are excreted.

ADA inhibition results in the metabolism of deoxyadenosine through an alternate pathway, whereby it is phosphorylated into the **toxic metabolite** deoxyadenosine triphosphate. Elevated intracellular levels of deoxyadenosine triphosphate activate the caspase system and also inhibit ribonucleotide reductase from converting ribonucleotides to deoxyribonucleotides, which depletes cells of DNA precursors. This ultimately results in the inhibition of DNA synthesis/repair and subsequent apoptosis.

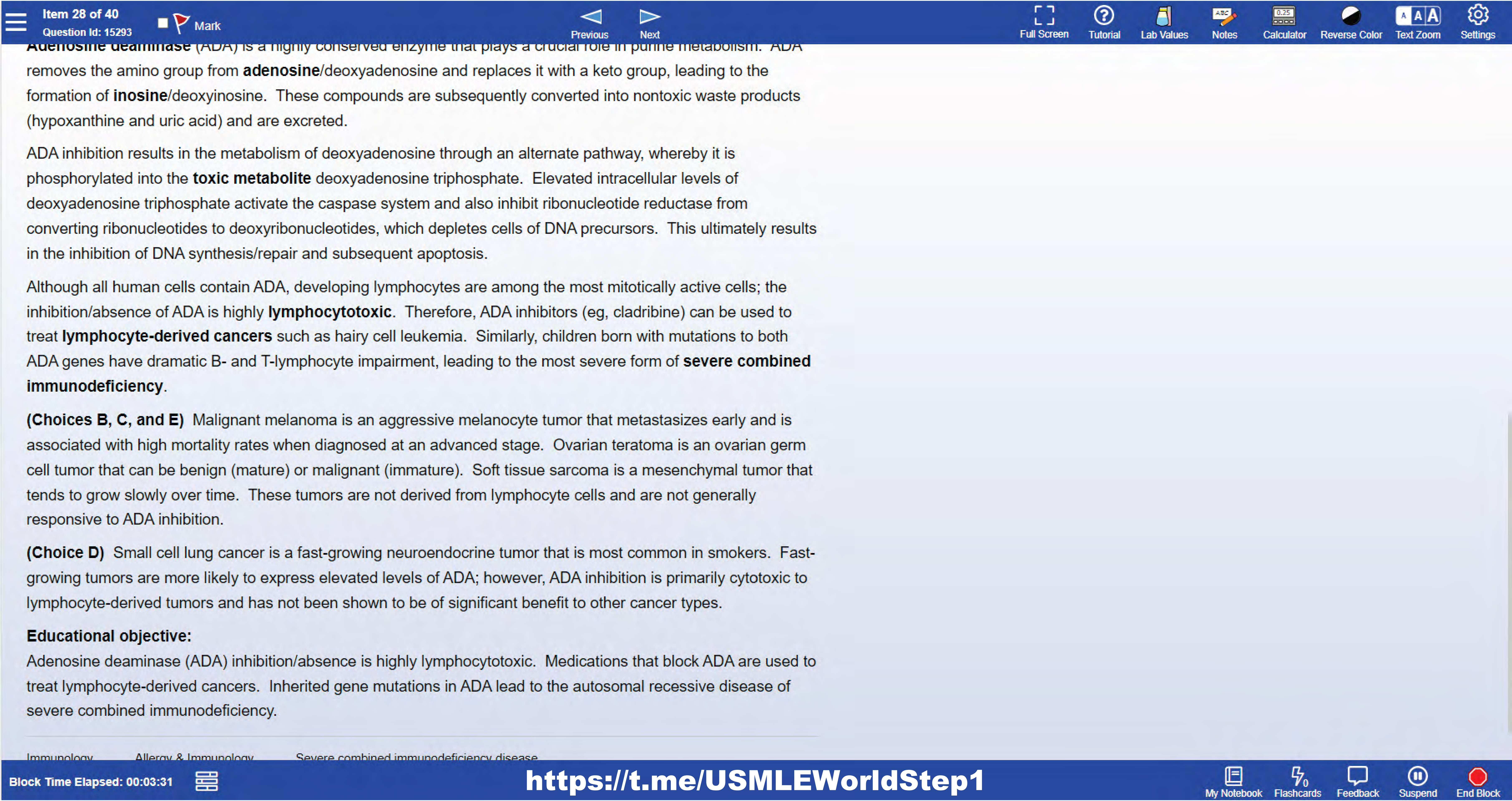
Although all human cells contain ADA, developing lymphocytes are among the most mitotically active cells; the inhibition/absence of ADA is highly **lymphocytotoxic**. Therefore, ADA inhibitors (eg, cladribine) can be used to treat **lymphocyte-derived cancers** such as hairy cell leukemia. Similarly, children born with mutations to both ADA genes have dramatic B- and T-lymphocyte impairment, leading to the most severe form of **severe combined immunodeficiency**.

(Choices B, C, and E) Malignant melanoma is an aggressive melanocyte tumor that metastasizes early and is associated with high mortality rates when diagnosed at an advanced stage. Ovarian teratoma is an ovarian germ cell tumor that can be benign (mature) or malignant (immature). Soft tissue sarcoma is a mesenchymal tumor that tends to grow slowly over time. These tumors are not derived from lymphocyte cells and are not generally responsive to ADA inhibition.

(Choice D) Small cell lung cancer is a fast-growing neuroendocrine tumor that is most common in smokers. Fast-growing tumors are more likely to express elevated levels of ADA; however, ADA inhibition is primarily cytotoxic to lymphocyte-derived tumors and has not been shown to be of significant benefit to other cancer types.

Educational objective:

Adenosine deaminase (ADA) inhibition/absence is highly lymphocytotoxic. Medications that block ADA are used to



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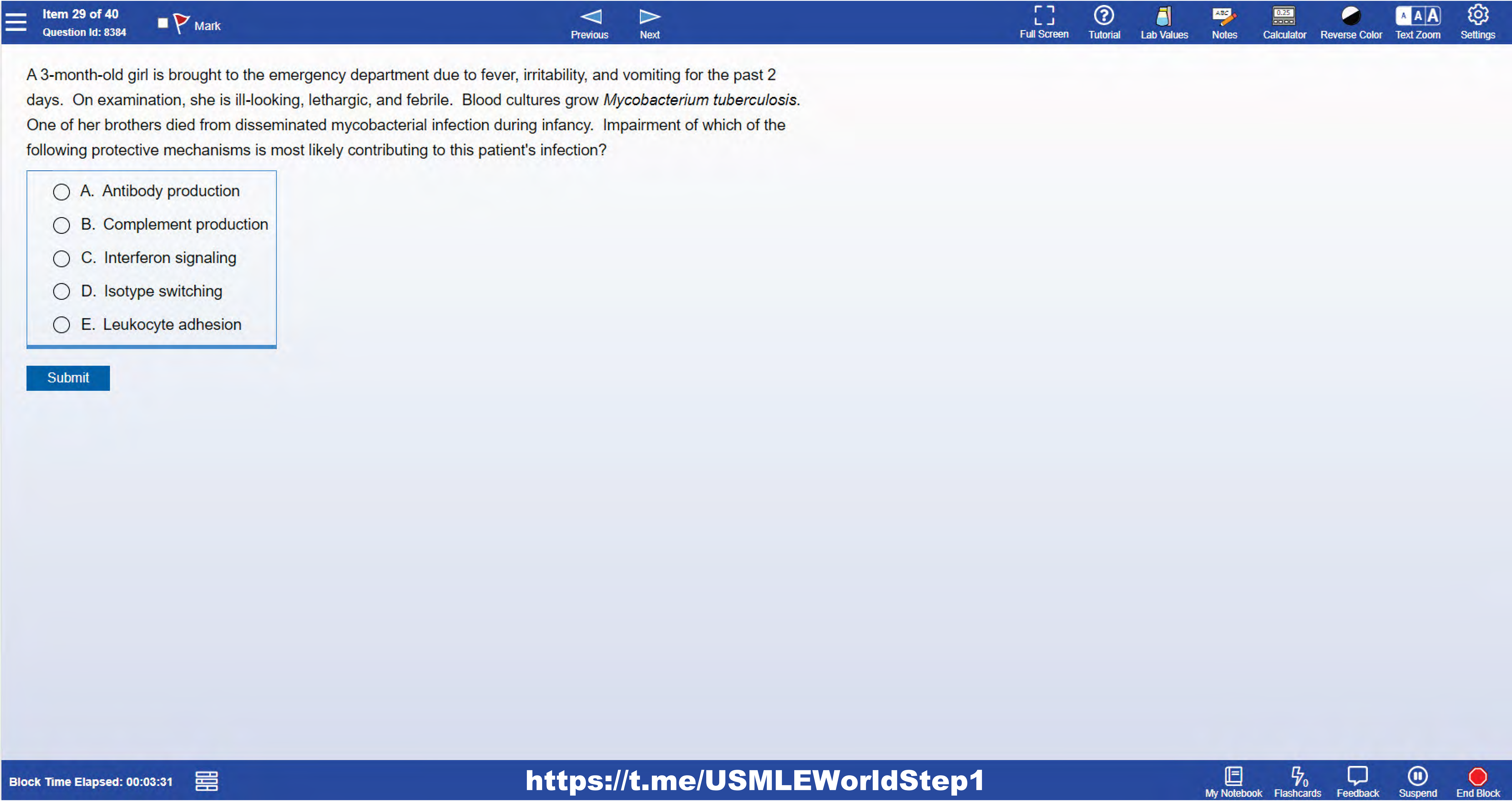
Educational objective:
Adenosine deaminase (ADA) inhibition/absence is highly lymphocytotoxic. Medications that block ADA are used to treat lymphocyte-derived cancers. Inherited gene mutations in ADA lead to the autosomal recessive disease of severe combined immunodeficiency.

Immunology | Allergy & Immunology | Severe combined immunodeficiency disease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A 3-month-old girl is brought to the emergency department due to fever, irritability, and vomiting for the past 2 days. On examination, she is ill-looking, lethargic, and febrile. Blood cultures grow *Mycobacterium tuberculosis*. One of her brothers died from disseminated mycobacterial infection during infancy. Impairment of which of the following protective mechanisms is most likely contributing to this patient's infection?

○ A. Antibody production
○ B. Complement production
○ C. Interferon signaling
○ D. Isotype switching
○ E. Leukocyte adhesion

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- ✗ ● A. Antibody production (4%)
- ○ B. Complement production (8%)
- ✓ ○ C. Interferon signaling (75%)
- ○ D. Isotype switching (3%)
- ○ E. Leukocyte adhesion (7%)

Incorrect
Correct answer
C

75%
Answered correctly

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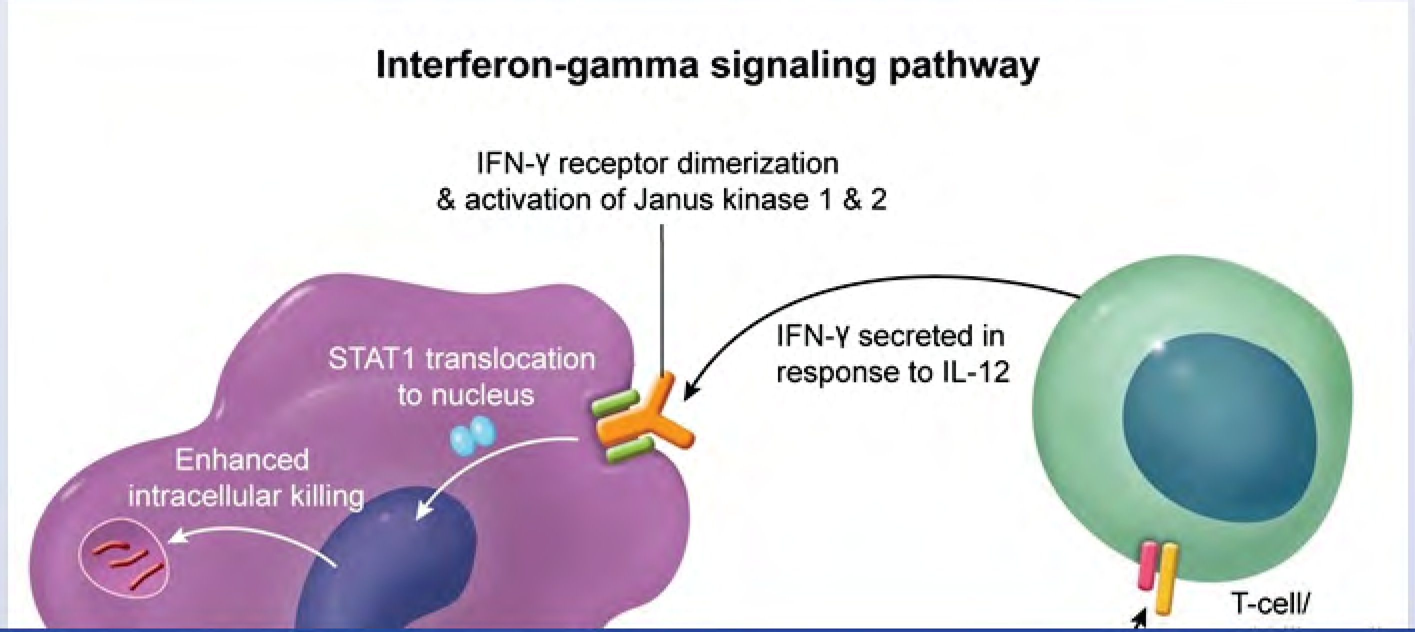
Explanation


Interferon-gamma signaling pathway
IFN-ɣ receptor dimerization
& activation of Janus kinase 1 & 2
IFN-ɣ secreted in
response to IL-12
STAT1 translocation
to nucleus
Enhanced
intracellular killing
T-cell/

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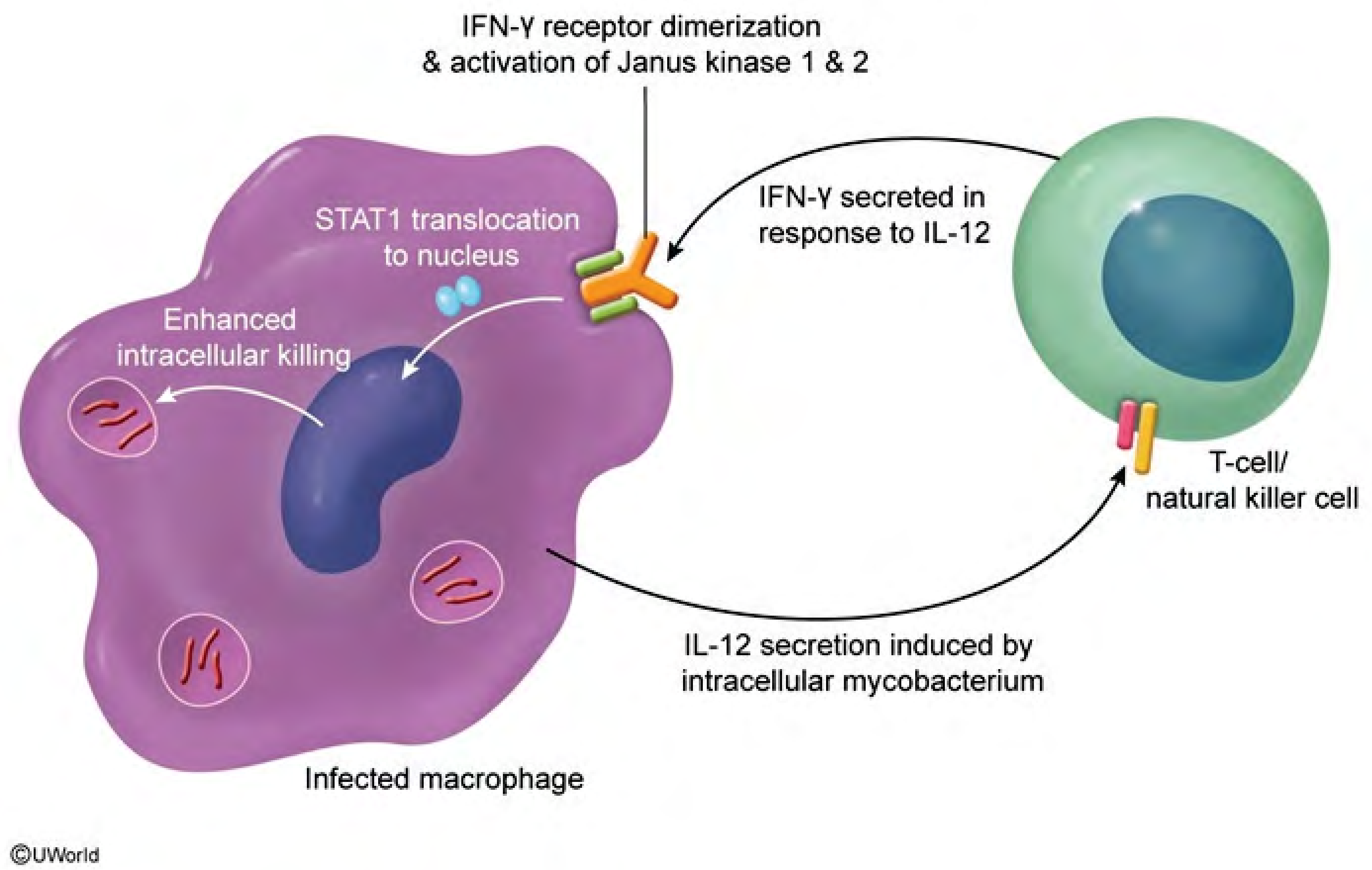
Interferon-gamma signaling pathway


IFN-Y receptor dimerization
& activation of Janus kinase 1 & 2
STAT1 translocation
to nucleus
IFN-Y secreted in
response to IL-12
Enhanced
intracellular killing
T-cell/
natural killer cell
IL-12 secretion induced by
intracellular mycobacterium
Infected macrophage

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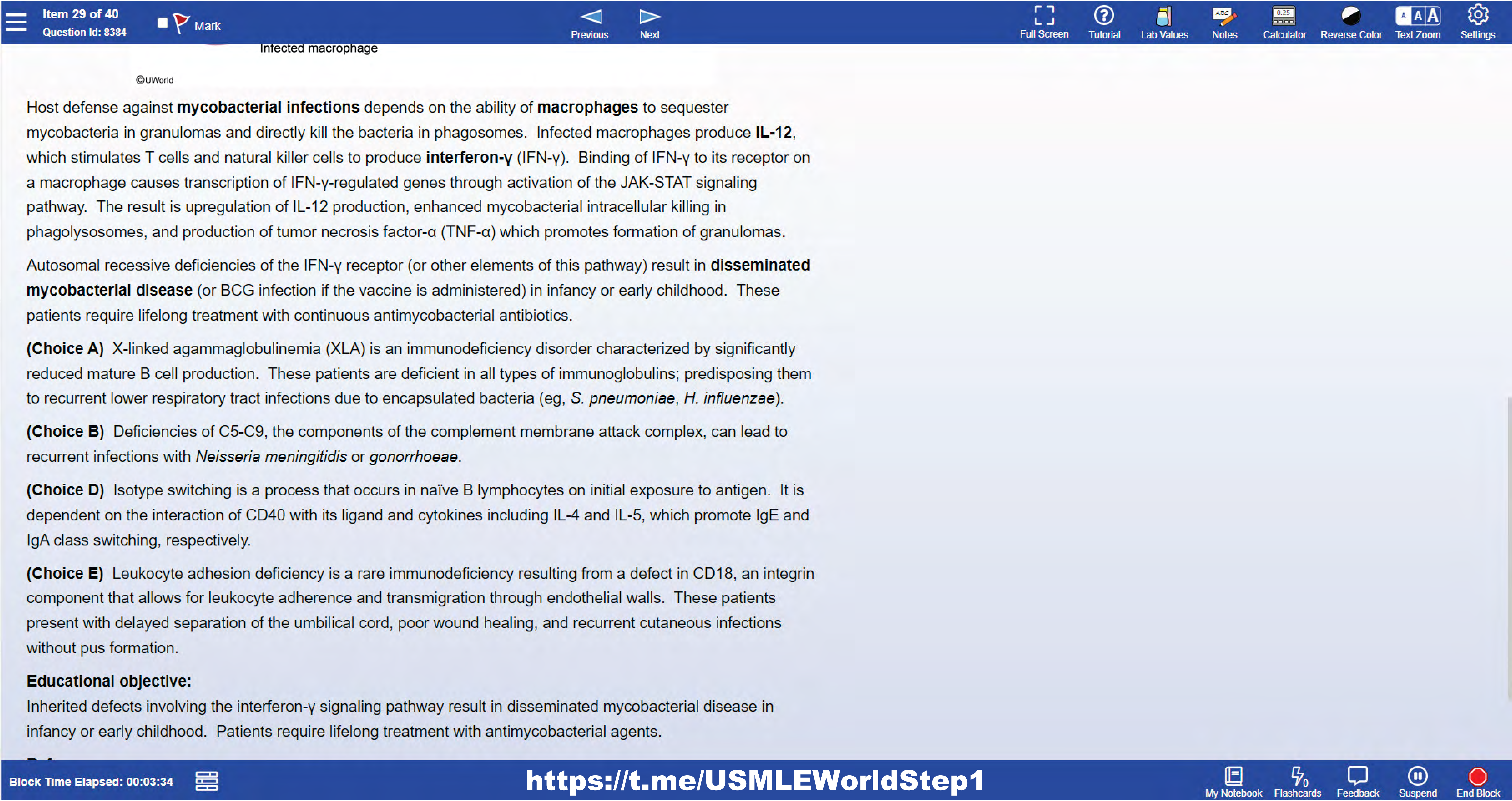
patients require lifelong treatment with continuous antimycobacterial antibiotics.



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Host defense against **mycobacterial infections** depends on the ability of **macrophages** to sequester mycobacteria in granulomas and directly kill the bacteria in phagosomes. Infected macrophages produce **IL-12**, which stimulates T cells and natural killer cells to produce **interferon-γ** (IFN-γ). Binding of IFN-γ to its receptor on a macrophage causes transcription of IFN-γ-regulated genes through activation of the JAK-STAT signaling pathway. The result is upregulation of IL-12 production, enhanced mycobacterial intracellular killing in phagolysosomes, and production of tumor necrosis factor-α (TNF-α) which promotes formation of granulomas.

Autosomal recessive deficiencies of the IFN-γ receptor (or other elements of this pathway) result in **disseminated mycobacterial disease** (or BCG infection if the vaccine is administered) in infancy or early childhood. These patients require lifelong treatment with continuous antimycobacterial antibiotics.

(Choice A) X-linked agammaglobulinemia (XLA) is an immunodeficiency disorder characterized by significantly reduced mature B cell production. These patients are deficient in all types of immunoglobulins; predisposing them to recurrent lower respiratory tract infections due to encapsulated bacteria (eg, *S. pneumoniae*, *H. influenzae*).

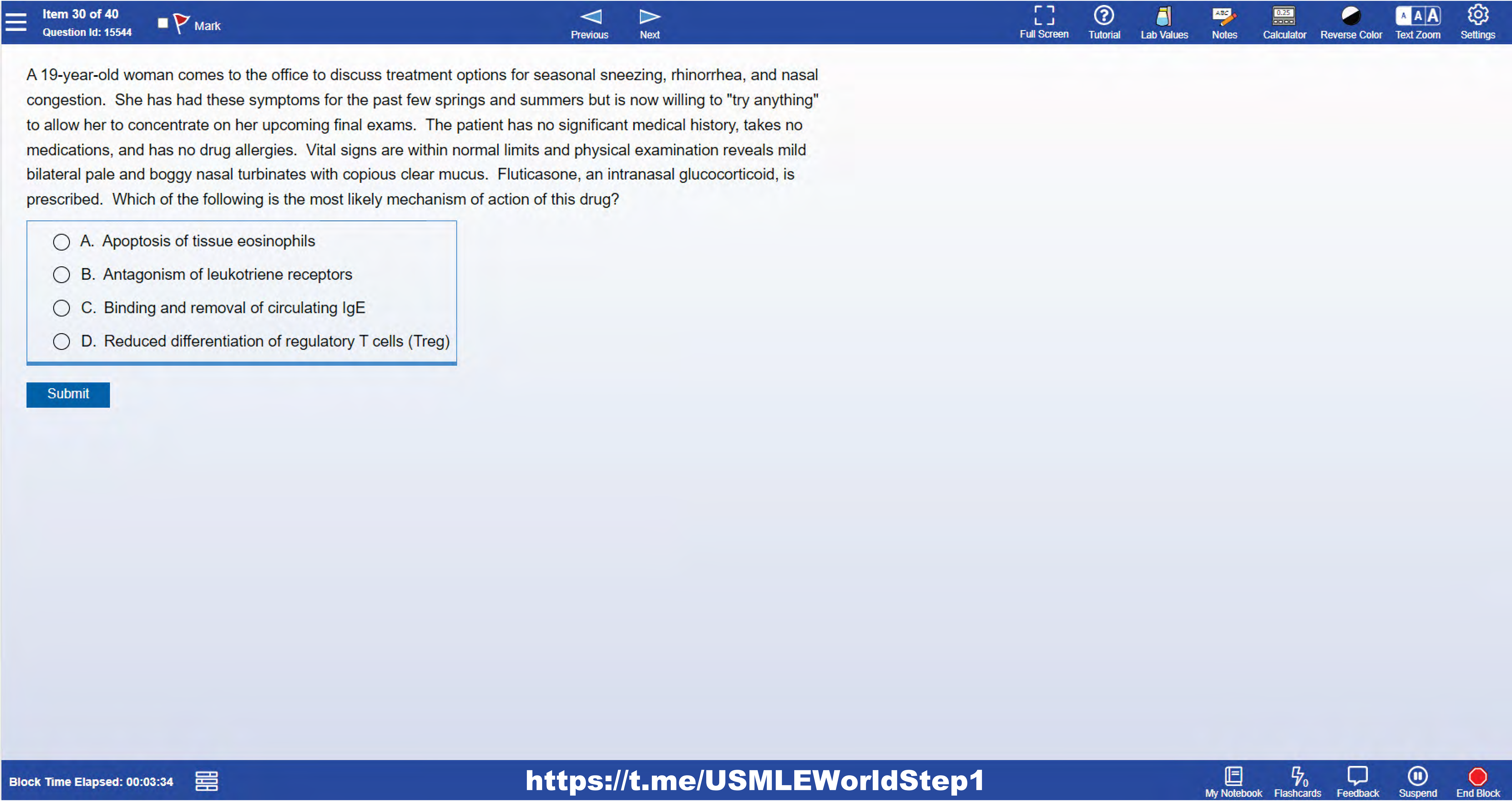
(Choice B) Deficiencies of C5-C9, the components of the complement membrane attack complex, can lead to recurrent infections with *Neisseria meningitidis* or *gonorrhoeae*.

(Choice D) Isotype switching is a process that occurs in naïve B lymphocytes on initial exposure to antigen. It is dependent on the interaction of CD40 with its ligand and cytokines including IL-4 and IL-5, which promote IgE and IgA class switching, respectively.

(Choice E) Leukocyte adhesion deficiency is a rare immunodeficiency resulting from a defect in CD18, an integrin component that allows for leukocyte adherence and transmigration through endothelial walls. These patients present with delayed separation of the umbilical cord, poor wound healing, and recurrent cutaneous infections without pus formation.

Educational objective:

Inherited defects involving the interferon-γ signaling pathway result in disseminated mycobacterial disease in infancy or early childhood. Patients require lifelong treatment with antimycobacterial agents.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A 19-year-old woman comes to the office to discuss treatment options for seasonal sneezing, rhinorrhea, and nasal congestion. She has had these symptoms for the past few springs and summers but is now willing to "try anything" to allow her to concentrate on her upcoming final exams. The patient has no significant medical history, takes no medications, and has no drug allergies. Vital signs are within normal limits and physical examination reveals mild bilateral pale and boggy nasal turbinates with copious clear mucus. Fluticasone, an intranasal glucocorticoid, is prescribed. Which of the following is the most likely mechanism of action of this drug?

- ○ A. Apoptosis of tissue eosinophils
- ○ B. Antagonism of leukotriene receptors
- ○ C. Binding and removal of circulating IgE
- ○ D. Reduced differentiation of regulatory T cells (Treg)

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- ✓ ● A. Apoptosis of tissue eosinophils (29%)
- ○ B. Antagonism of leukotriene receptors (32%)
- ○ C. Binding and removal of circulating IgE (12%)
- ○ D. Reduced differentiation of regulatory T cells (Treg) (25%)

Correct

29% Answered correctly

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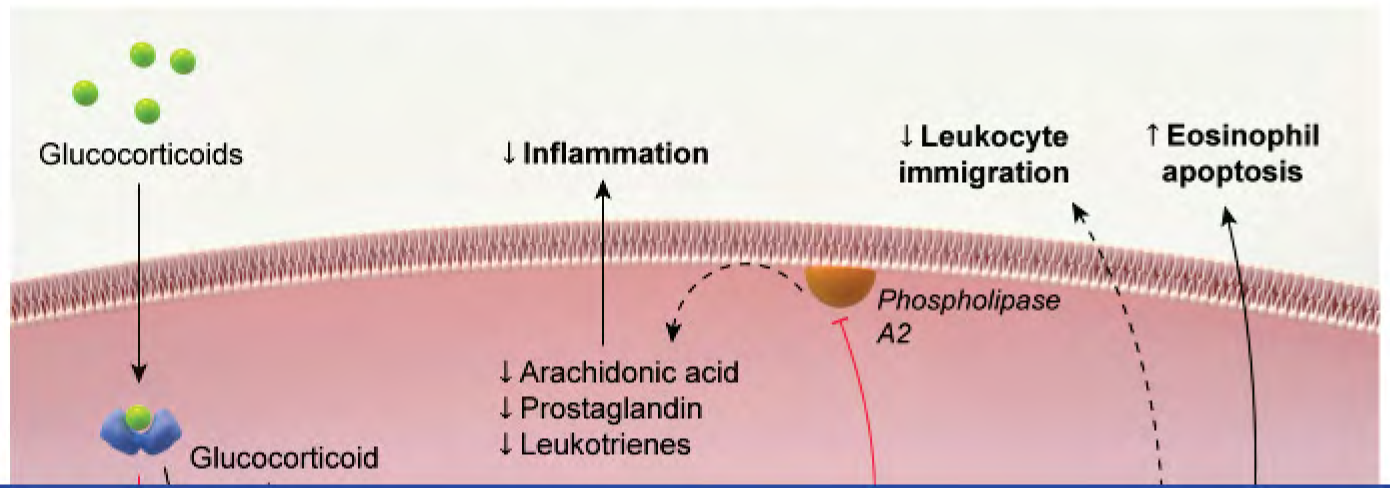
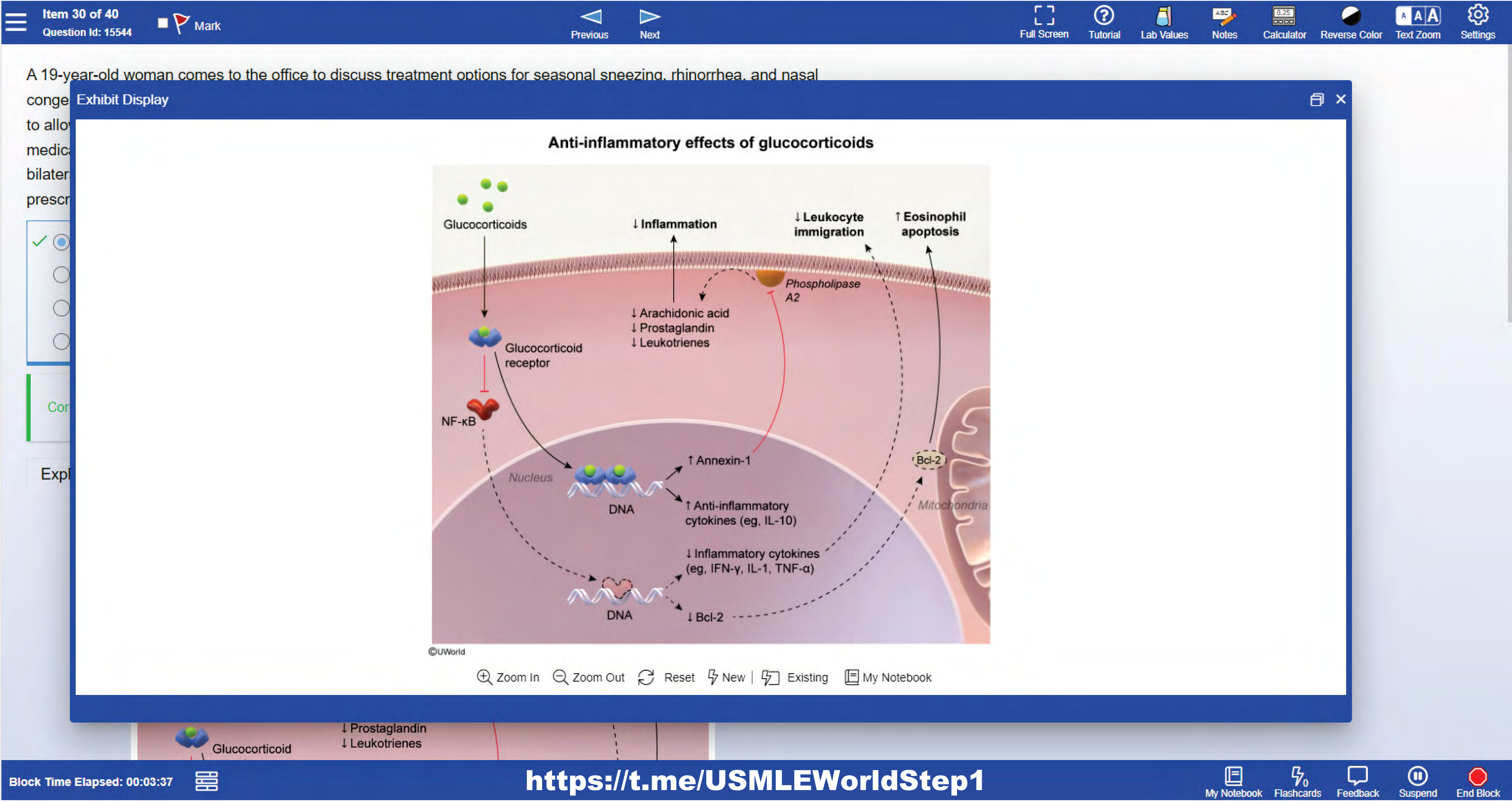
2023 Version

Explanation

Anti-inflammatory effects of glucocorticoids


Glucocorticoids
↓ Inflammation
↓ Leukocyte immigration
↑ Eosinophil apoptosis
Phospholipase A2
↓ Arachidonic acid
↓ Prostaglandin
↓ Leukotrienes
Glucocorticoid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Anti-inflammatory effects of glucocorticoids

Glucocorticoids
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↓ Leukocyte immigration
↑ Eosinophil apoptosis
Phospholipase A2
↓ Arachidonic acid
↓ Prostaglandin
↓ Leukotrienes
Glucocorticoid receptor
NF-κB
Nucleus
DNA
↑ Annexin-1
↑ Anti-inflammatory cytokines (eg, IL-10)
↓ Inflammatory cytokines (eg, IFN-γ, IL-1, TNF-α)
DNA
↓ Bcl-2
Bcl-2
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↓ Prostaglandin
↓ Leukotrienes
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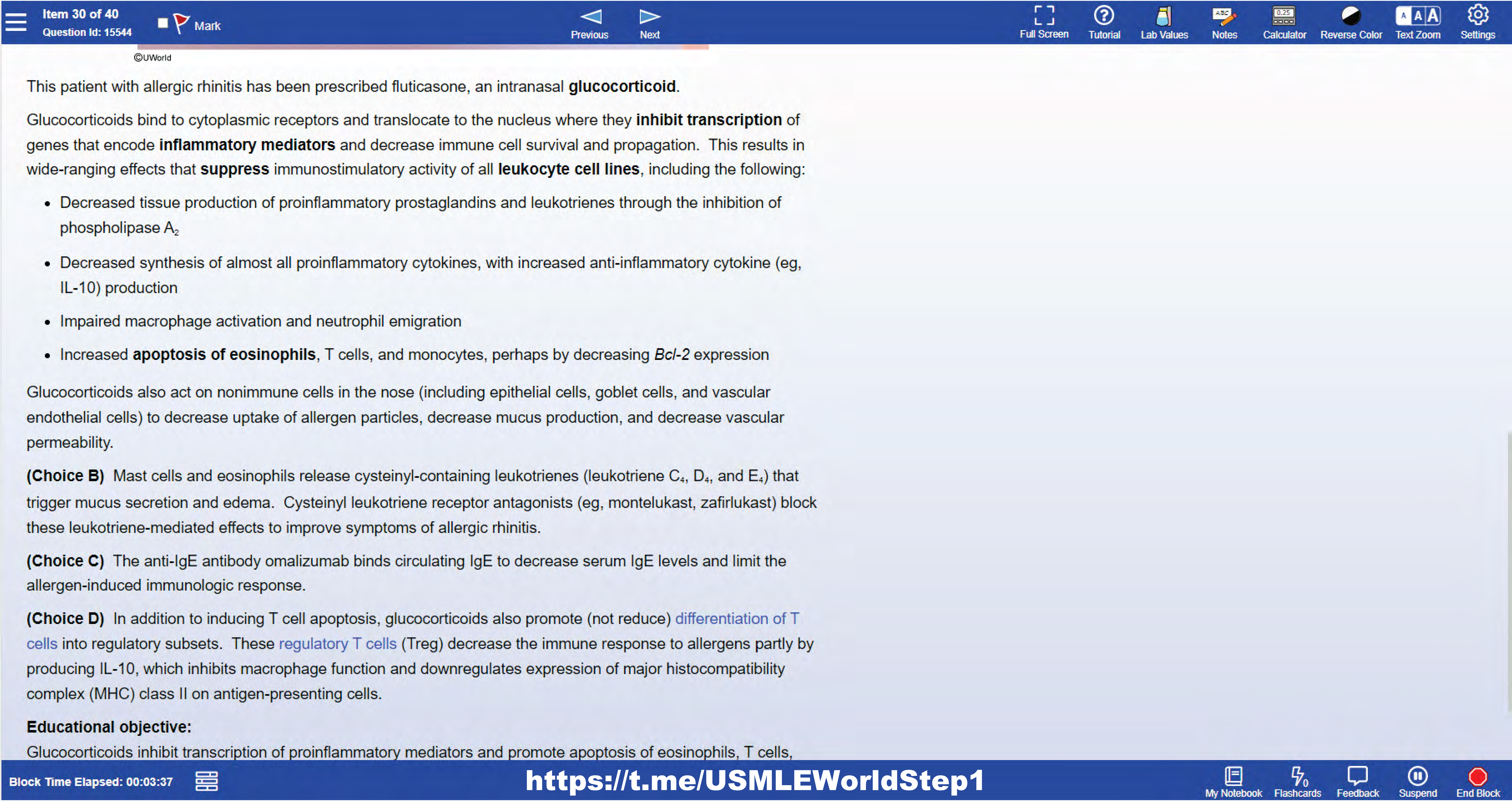

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This patient with allergic rhinitis has been prescribed fluticasone, an intranasal **glucocorticoid**.

Glucocorticoids bind to cytoplasmic receptors and translocate to the nucleus where they **inhibit transcription** of genes that encode **inflammatory mediators** and decrease immune cell survival and propagation. This results in wide-ranging effects that **suppress** immunostimulatory activity of all **leukocyte cell lines**, including the following:

- Decreased tissue production of proinflammatory prostaglandins and leukotrienes through the inhibition of phospholipase A_2
- Decreased synthesis of almost all proinflammatory cytokines, with increased anti-inflammatory cytokine (eg, IL-10) production
- Impaired macrophage activation and neutrophil emigration
- Increased **apoptosis of eosinophils**, T cells, and monocytes, perhaps by decreasing *Bcl-2* expression

Glucocorticoids also act on nonimmune cells in the nose (including epithelial cells, goblet cells, and vascular endothelial cells) to decrease uptake of allergen particles, decrease mucus production, and decrease vascular permeability.

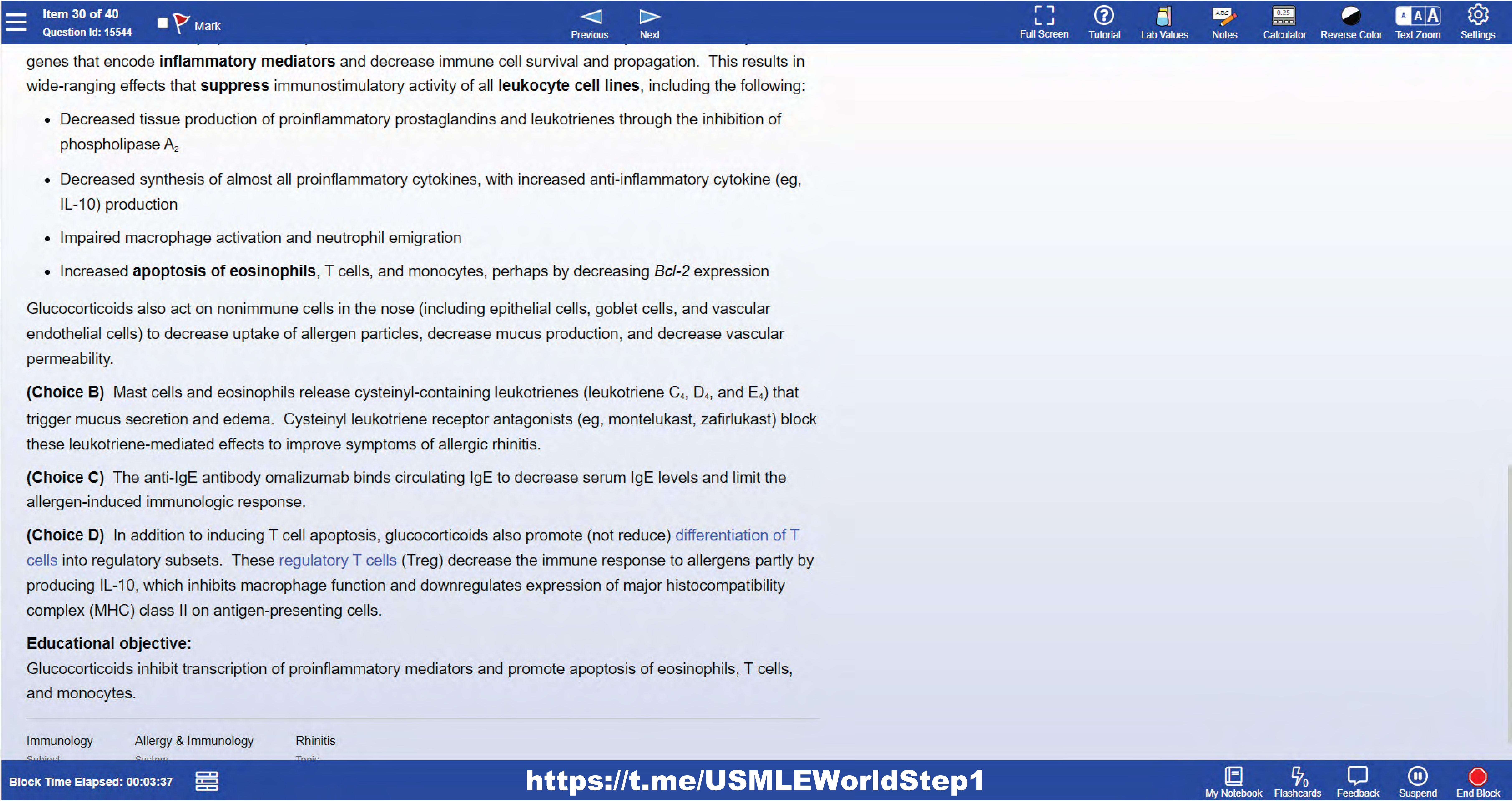
(Choice B) Mast cells and eosinophils release cysteinyl-containing leukotrienes (leukotriene C_4, D_4, and E_4) that trigger mucus secretion and edema. Cysteinyl leukotriene receptor antagonists (eg, montelukast, zafirlukast) block these leukotriene-mediated effects to improve symptoms of allergic rhinitis.

(Choice C) The anti-IgE antibody omalizumab binds circulating IgE to decrease serum IgE levels and limit the allergen-induced immunologic response.

(Choice D) In addition to inducing T cell apoptosis, glucocorticoids also promote (not reduce) differentiation of T cells into regulatory subsets. These regulatory T cells (Treg) decrease the immune response to allergens partly by producing IL-10, which inhibits macrophage function and downregulates expression of major histocompatibility complex (MHC) class II on antigen-presenting cells.

Educational objective:

Glucocorticoids inhibit transcription of proinflammatory mediators and promote apoptosis of eosinophils, T cells,



genes that encode **inflammatory mediators** and decrease immune cell survival and propagation. This results in wide-ranging effects that **suppress** immunostimulatory activity of all **leukocyte cell lines**, including the following:

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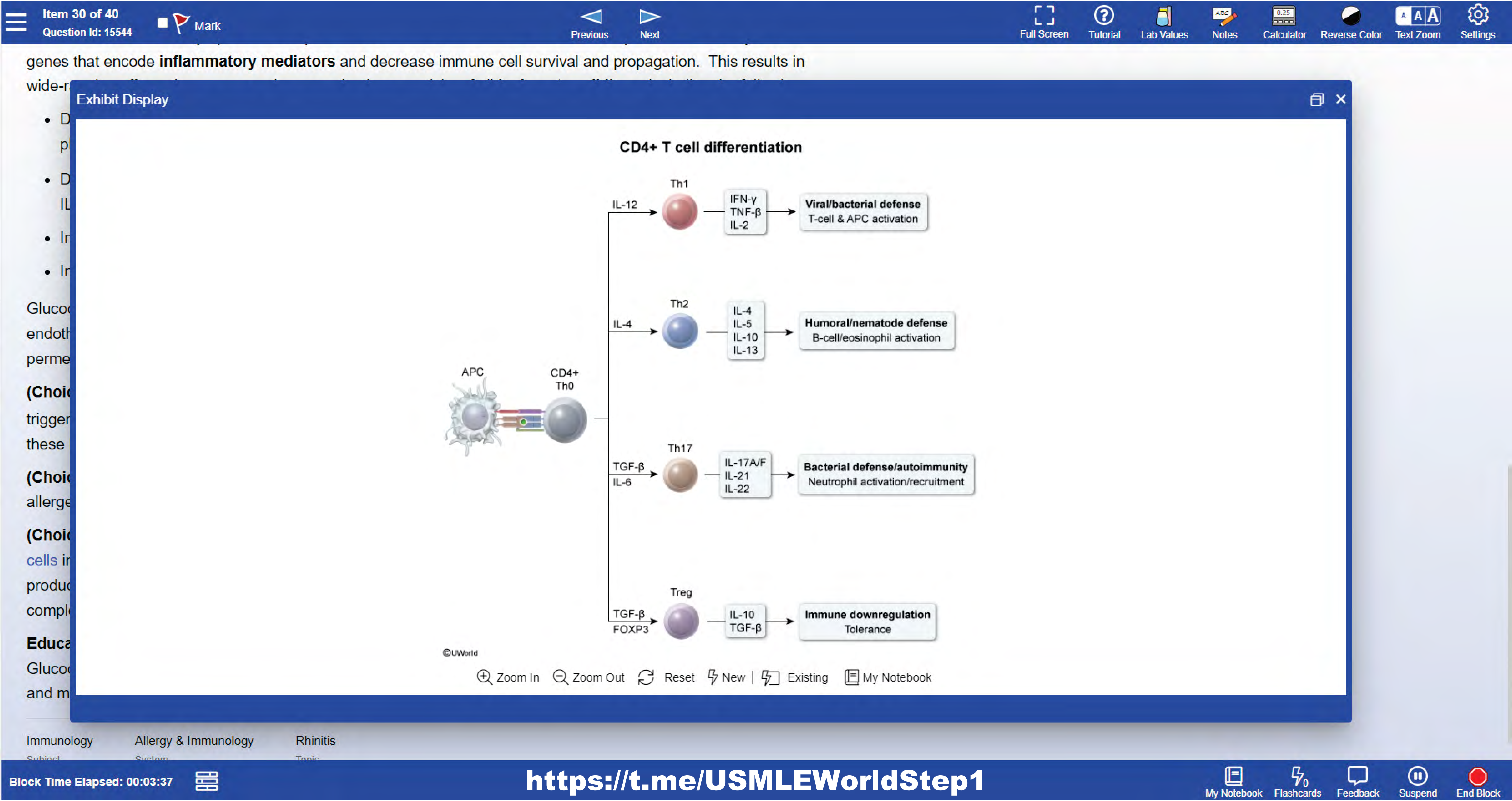
Immunology	Allergy & Immunology	Rhinitis
Subject	System	Topic



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CD4+ T cell differentiation

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CD4+
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IL-12
Th1
IFN-γ
TNF-β
IL-2
Viral/bacterial defense
T-cell & APC activation
IL-4
Th2
IL-4
IL-5
IL-10
IL-13
Humoral/nematode defense
B-cell/eosinophil activation
TGF-β
IL-6
Th17
IL-17A/F
IL-21
IL-22
Bacterial defense/autoimmunity
Neutrophil activation/recruitment
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FOXP3
Treg
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Immunology
Subject

Allergy & Immunology
System

Rhinitis
Topic

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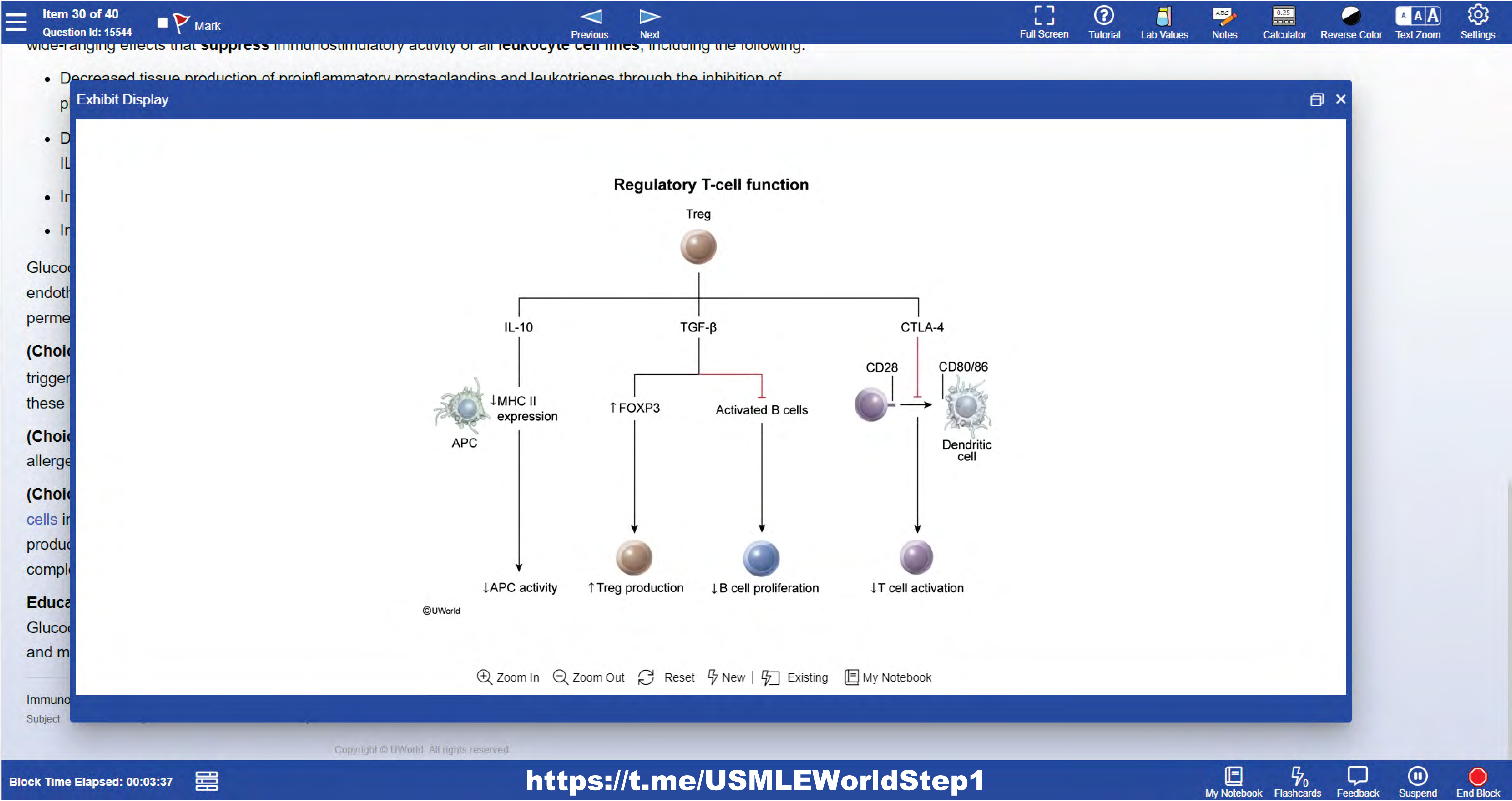

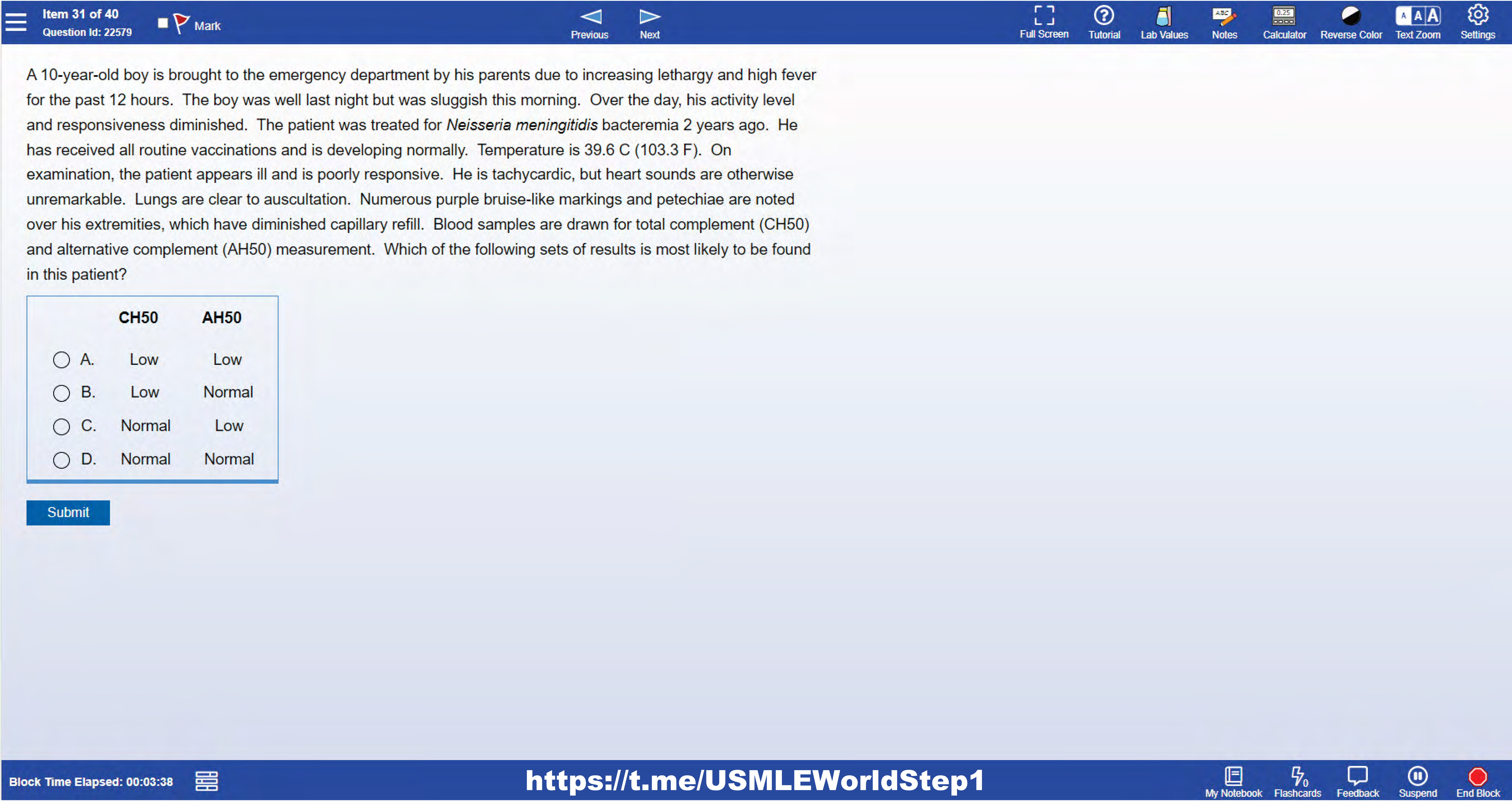
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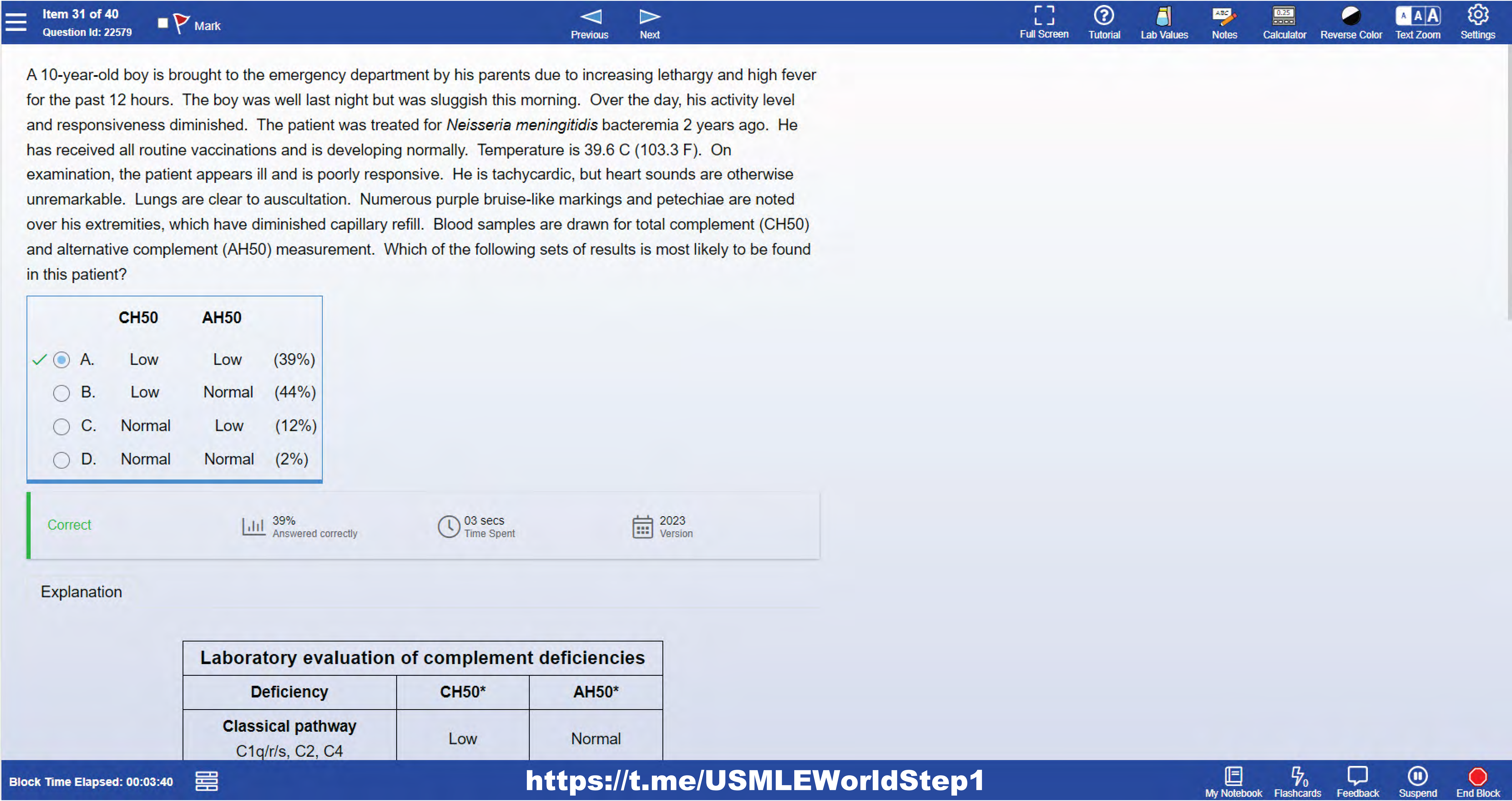
A 10-year-old boy is brought to the emergency department by his parents due to increasing lethargy and high fever for the past 12 hours. The boy was well last night but was sluggish this morning. Over the day, his activity level and responsiveness diminished. The patient was treated for *Neisseria meningitidis* bacteremia 2 years ago. He has received all routine vaccinations and is developing normally. Temperature is 39.6 C (103.3 F). On examination, the patient appears ill and is poorly responsive. He is tachycardic, but heart sounds are otherwise unremarkable. Lungs are clear to auscultation. Numerous purple bruise-like markings and petechiae are noted over his extremities, which have diminished capillary refill. Blood samples are drawn for total complement (CH50) and alternative complement (AH50) measurement. Which of the following sets of results is most likely to be found in this patient?

	CH50	**AH50**
○ A.	Low	Low
○ B.	Low	Normal
○ C.	Normal	Low
○ D.	Normal	Normal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	CH50	**AH50**	
✓ ● A.	Low	Low	(39%)
○ B.	Low	Normal	(44%)
○ C.	Normal	Low	(12%)
○ D.	Normal	Normal	(2%)

Correct

39%
Answered correctly

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Explanation

Laboratory evaluation of complement deficiencies		
Deficiency	**CH50***	**AH50***
Classical pathway C1q/r/s, C2, C4	Low	Normal

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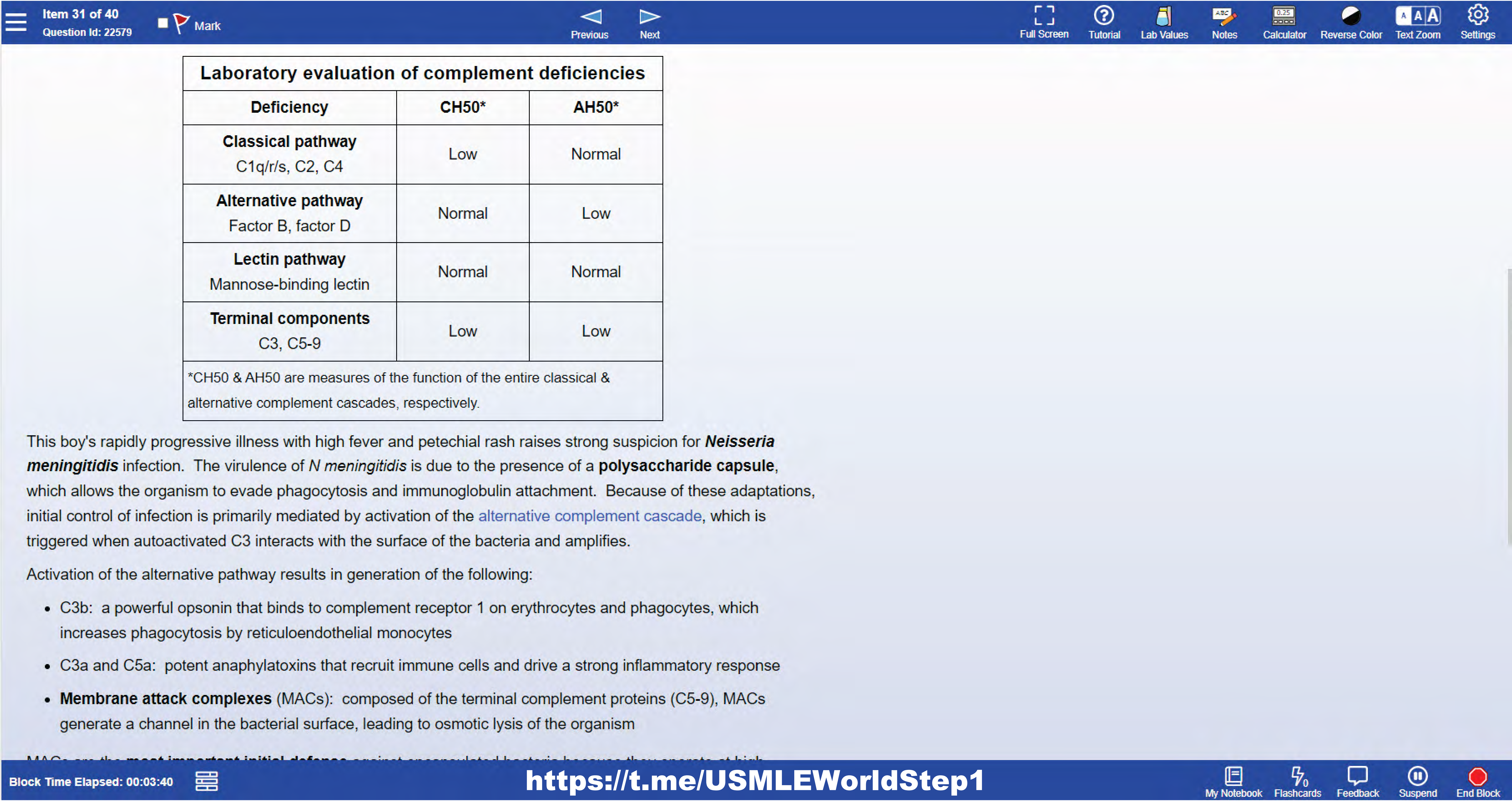
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Laboratory evaluation of complement deficiencies		
Deficiency	**CH50***	**AH50***
Classical pathway C1q/r/s, C2, C4	Low	Normal
Alternative pathway Factor B, factor D	Normal	Low
Lectin pathway Mannose-binding lectin	Normal	Normal
Terminal components C3, C5-9	Low	Low
*CH50 & AH50 are measures of the function of the entire classical & alternative complement cascades, respectively.		

This boy's rapidly progressive illness with high fever and petechial rash raises strong suspicion for ***Neisseria meningitidis*** infection. The virulence of *N meningitidis* is due to the presence of a **polysaccharide capsule**, which allows the organism to evade phagocytosis and immunoglobulin attachment. Because of these adaptations, initial control of infection is primarily mediated by activation of the alternative complement cascade, which is triggered when autoactivated C3 interacts with the surface of the bacteria and amplifies.

Activation of the alternative pathway results in generation of the following:

- C3b: a powerful opsonin that binds to complement receptor 1 on erythrocytes and phagocytes, which increases phagocytosis by reticuloendothelial monocytes
- C3a and C5a: potent anaphylatoxins that recruit immune cells and drive a strong inflammatory response
- **Membrane attack complexes** (MACs): composed of the terminal complement proteins (C5-9), MACs generate a channel in the bacterial surface, leading to osmotic lysis of the organism

MACs are the **most important initial defense** against encapsulated bacteria because they operate at high

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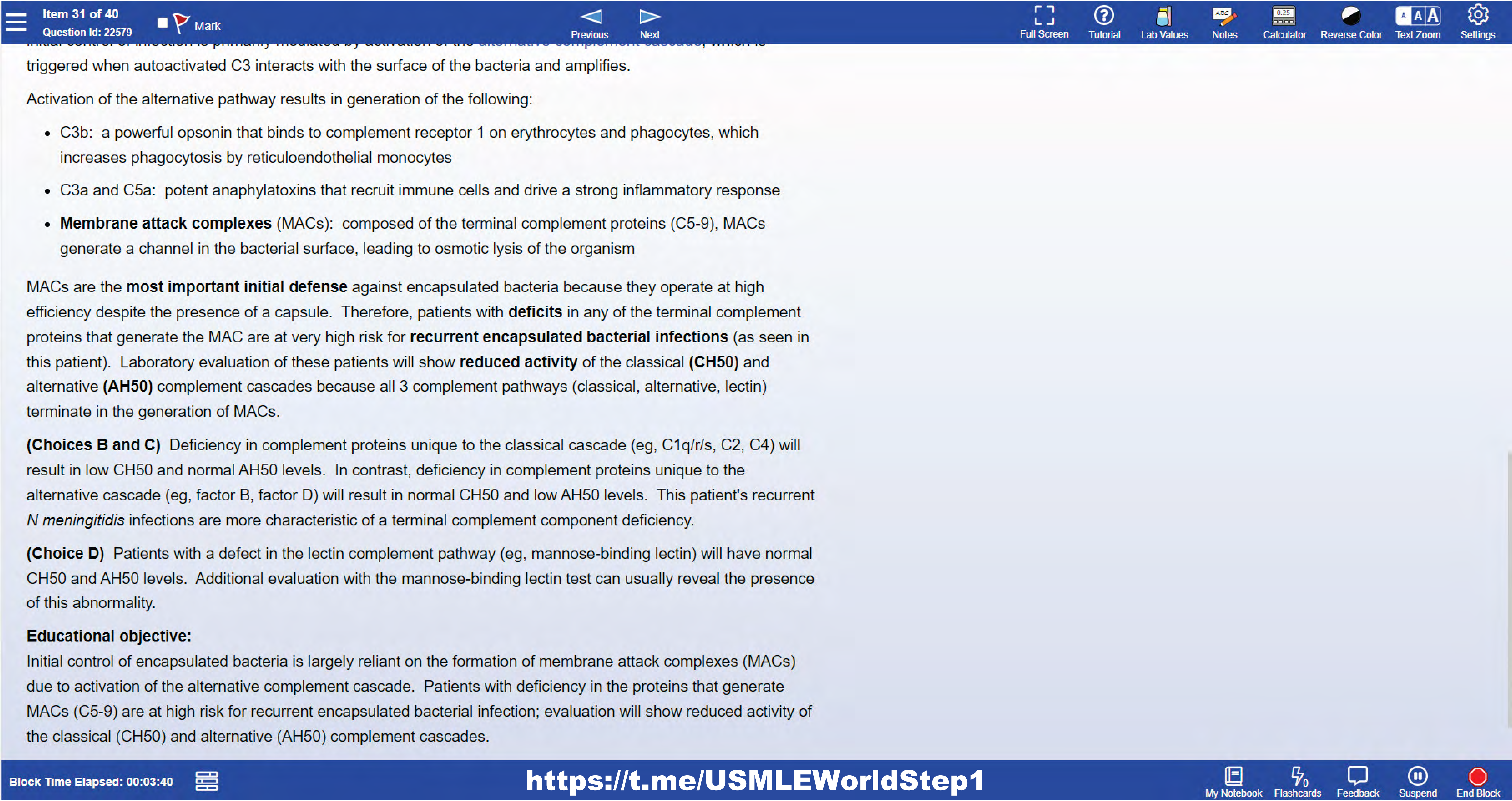

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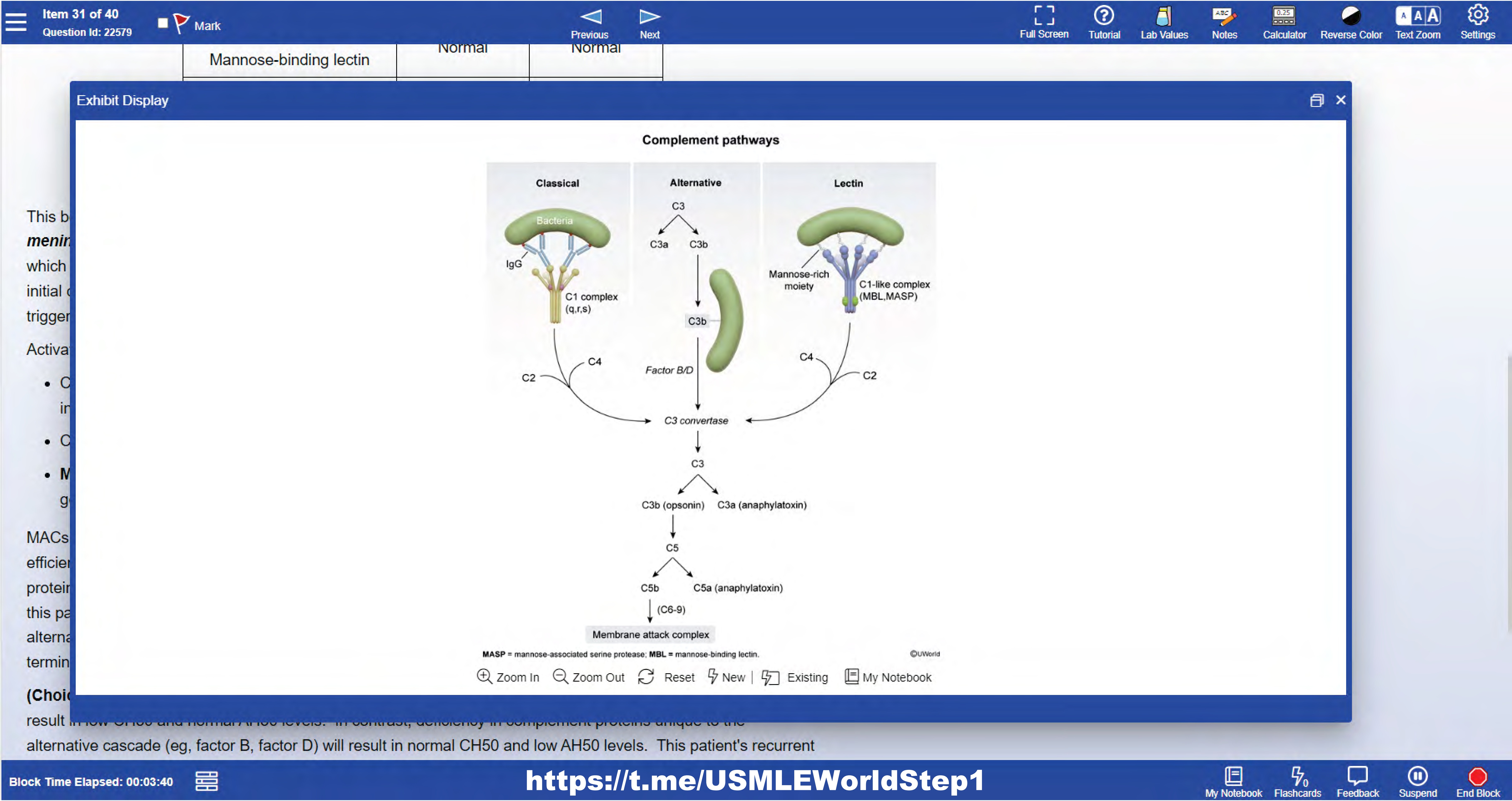
- **Membrane attack complexes** (MACs): composed of the terminal complement proteins (C5-9), MACs generate a channel in the bacterial surface, leading to osmotic lysis of the organism

MACs are the **most important initial defense** against encapsulated bacteria because they operate at high efficiency despite the presence of a capsule. Therefore, patients with **deficits** in any of the terminal complement proteins that generate the MAC are at very high risk for **recurrent encapsulated bacterial infections** (as seen in this patient). Laboratory evaluation of these patients will show **reduced activity** of the classical **(CH50)** and alternative **(AH50)** complement cascades because all 3 complement pathways (classical, alternative, lectin) terminate in the generation of MACs.

(Choices B and C) Deficiency in complement proteins unique to the classical cascade (eg, C1q/r/s, C2, C4) will result in low CH50 and normal AH50 levels. In contrast, deficiency in complement proteins unique to the alternative cascade (eg, factor B, factor D) will result in normal CH50 and low AH50 levels. This patient's recurrent *N meningitidis* infections are more characteristic of a terminal complement component deficiency.

(Choice D) Patients with a defect in the lectin complement pathway (eg, mannose-binding lectin) will have normal CH50 and AH50 levels. Additional evaluation with the mannose-binding lectin test can usually reveal the presence of this abnormality.

Educational objective:
Initial control of encapsulated bacteria is largely reliant on the formation of membrane attack complexes (MACs) due to activation of the alternative complement cascade. Patients with deficiency in the proteins that generate MACs (C5-9) are at high risk for recurrent encapsulated bacterial infection; evaluation will show reduced activity of the classical (CH50) and alternative (AH50) complement cascades.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result in low CH50 and normal AH50 levels. In contrast, deficiency in complement proteins unique to the alternative cascade (eg, factor B, factor D) will result in normal CH50 and low AH50 levels. This patient's recurrent

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Complement pathways

Classical
Bacteria
IgG
C1 complex (q,r,s)
C2
C4
Alternative
C3
C3a
C3b
C3b
Factor B/D
Lectin
Mannose-rich moiety
C1-like complex (MBL,MASP)
C4
C2
C3 convertase
C3
C3b (opsonin)
C3a (anaphylatoxin)
C5
C5b
C5a (anaphylatoxin)
(C6-9)
Membrane attack complex

MASP = mannose-associated serine protease; **MBL** = mannose-binding lectin.

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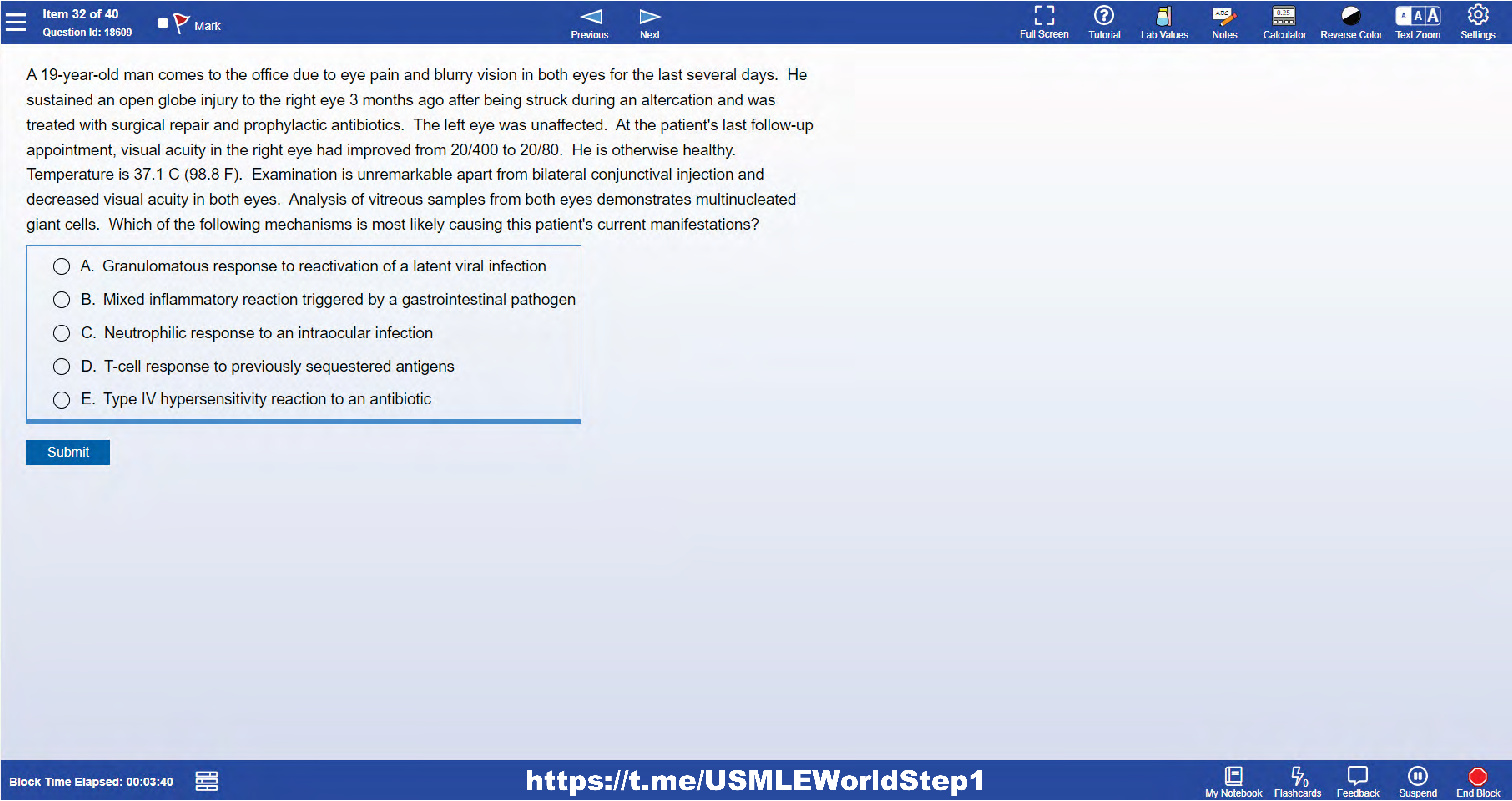
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Question Id: 18609
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A 19-year-old man comes to the office due to eye pain and blurry vision in both eyes for the last several days. He sustained an open globe injury to the right eye 3 months ago after being struck during an altercation and was treated with surgical repair and prophylactic antibiotics. The left eye was unaffected. At the patient's last follow-up appointment, visual acuity in the right eye had improved from 20/400 to 20/80. He is otherwise healthy. Temperature is 37.1 C (98.8 F). Examination is unremarkable apart from bilateral conjunctival injection and decreased visual acuity in both eyes. Analysis of vitreous samples from both eyes demonstrates multinucleated giant cells. Which of the following mechanisms is most likely causing this patient's current manifestations?

○ A. Granulomatous response to reactivation of a latent viral infection
○ B. Mixed inflammatory reaction triggered by a gastrointestinal pathogen
○ C. Neutrophilic response to an intraocular infection
○ D. T-cell response to previously sequestered antigens
○ E. Type IV hypersensitivity reaction to an antibiotic

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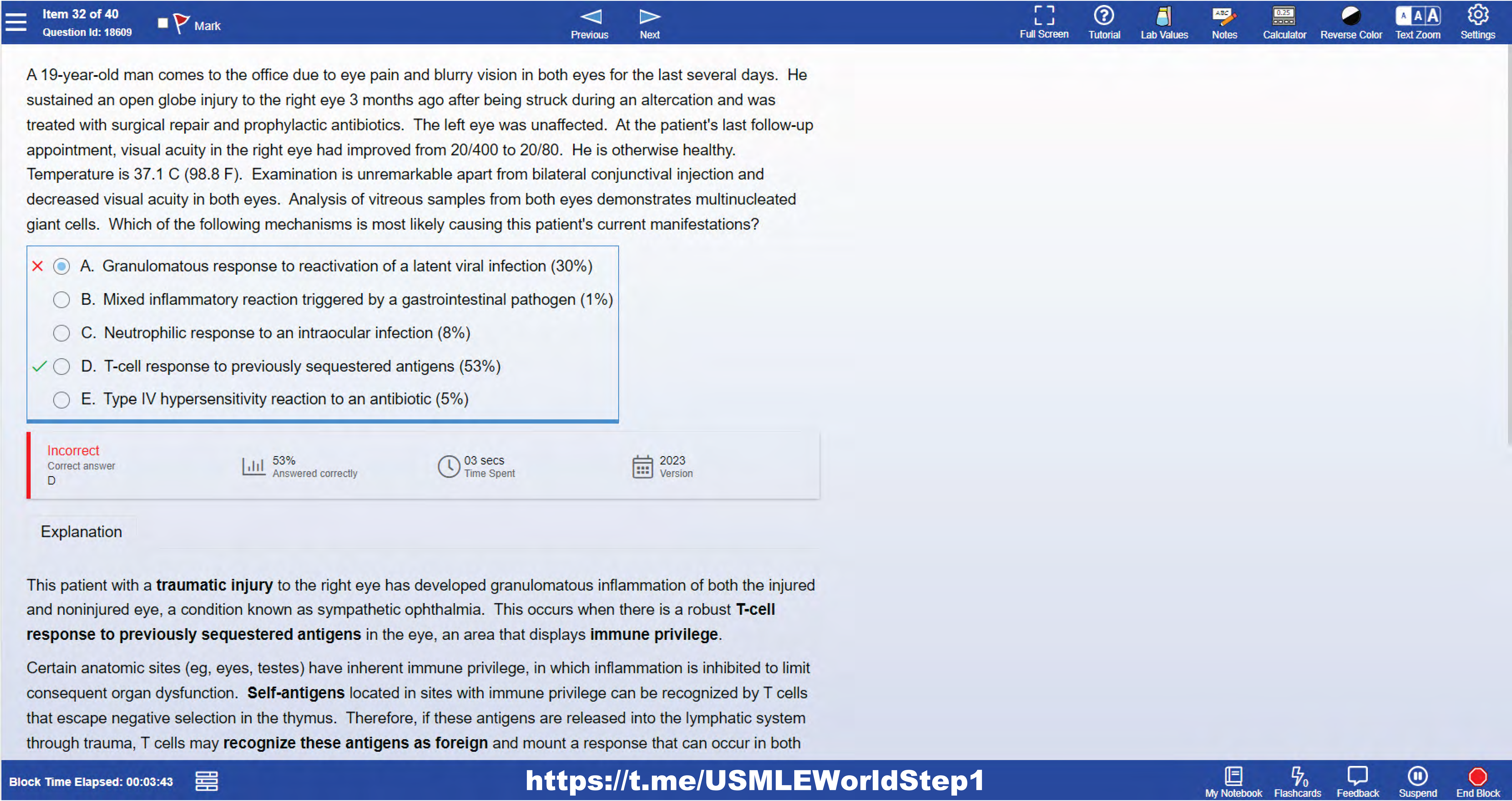

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✗ ● A. Granulomatous response to reactivation of a latent viral infection (30%)
○ B. Mixed inflammatory reaction triggered by a gastrointestinal pathogen (1%)
○ C. Neutrophilic response to an intraocular infection (8%)
✓ ○ D. T-cell response to previously sequestered antigens (53%)
○ E. Type IV hypersensitivity reaction to an antibiotic (5%)

Incorrect
Correct answer
D

53%
Answered correctly

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Explanation

This patient with a **traumatic injury** to the right eye has developed granulomatous inflammation of both the injured and noninjured eye, a condition known as sympathetic ophthalmia. This occurs when there is a robust **T-cell response to previously sequestered antigens** in the eye, an area that displays **immune privilege**.

Certain anatomic sites (eg, eyes, testes) have inherent immune privilege, in which inflammation is inhibited to limit consequent organ dysfunction. **Self-antigens** located in sites with immune privilege can be recognized by T cells that escape negative selection in the thymus. Therefore, if these antigens are released into the lymphatic system through trauma, T cells may **recognize these antigens as foreign** and mount a response that can occur in both

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This patient with a **traumatic injury** to the right eye has developed granulomatous inflammation of both the injured and noninjured eye, a condition known as sympathetic ophthalmia. This occurs when there is a robust **T-cell response to previously sequestered antigens** in the eye, an area that displays **immune privilege**.

Certain anatomic sites (eg, eyes, testes) have inherent immune privilege, in which inflammation is inhibited to limit consequent organ dysfunction. **Self-antigens** located in sites with immune privilege can be recognized by T cells that escape negative selection in the thymus. Therefore, if these antigens are released into the lymphatic system through trauma, T cells may **recognize these antigens as foreign** and mount a response that can occur in both the injured eye and the **contralateral eye**.

Because of this potential sight-threatening condition, if an eye is severely injured with no prognosis for recovery of vision, it is surgically removed (ie, enucleated) to prevent **blindness in the uninjured eye**. However, in patients whose vision is likely to recover, treatment is focused on decreasing inflammation (eg, corticosteroids) should the condition develop.

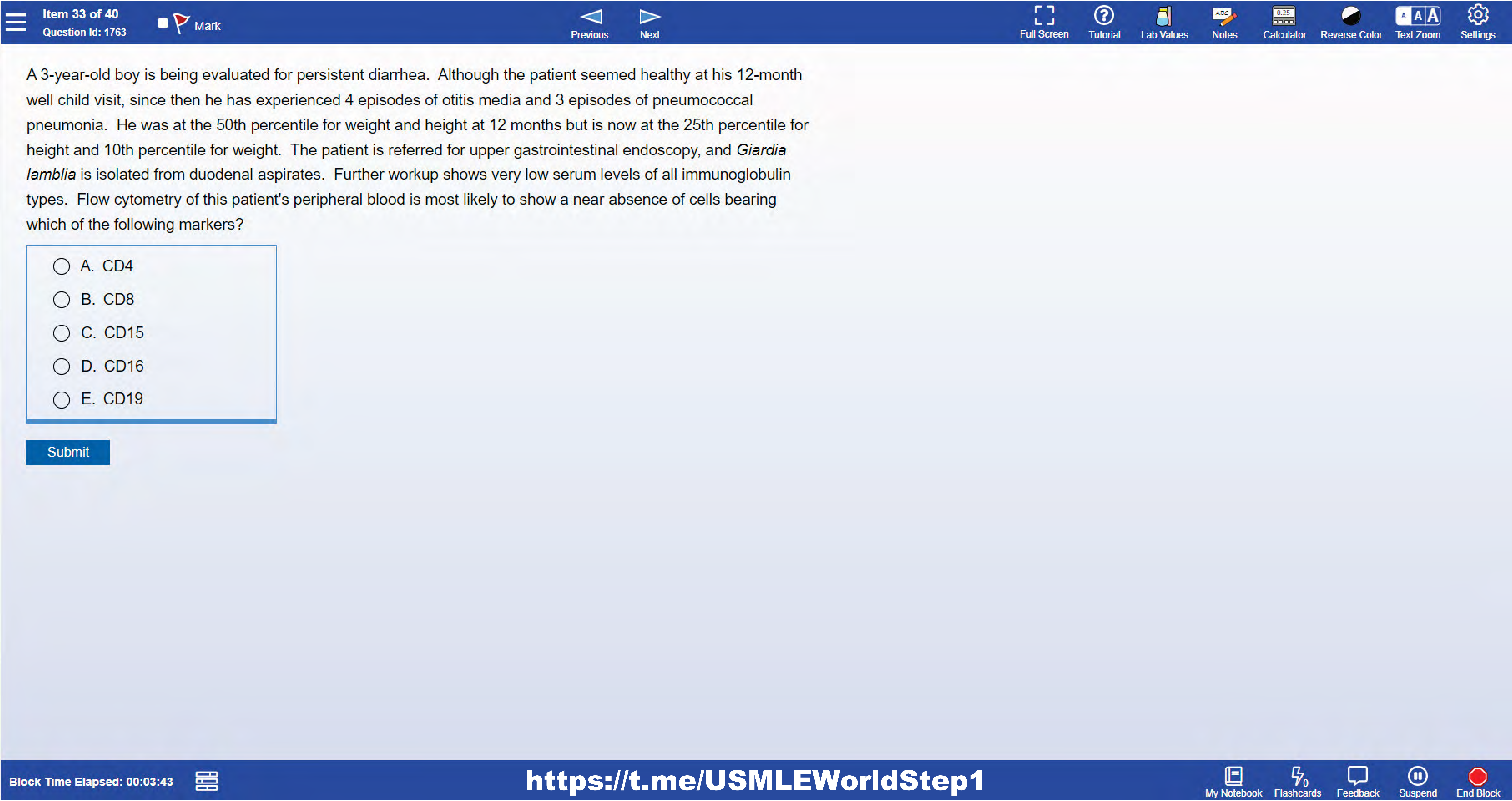
(Choice A) Herpes zoster reactivation can cause granulomatous keratouveitis (ie, anterior chamber inflammation). However, herpes zoster typically reactivates in a single ganglion, leading to unilateral symptoms.

(Choice B) Spondyloarthritis may be triggered by a gastrointestinal pathogen and result in a mixed inflammatory reaction that leads to reactive arthritis and uveitis. However, it is not triggered by previous ocular trauma.

(Choice C) Infectious agents can be introduced during trauma or surgery, which can result in an acute intraocular infection that prompts a neutrophilic response. However, this would not affect the contralateral eye.

(Choice E) Although rare, a type IV hypersensitivity reaction to an antibiotic may cause bilateral uveitis. However, this would occur near the time of antibiotic administration, not 3 months later.

Educational objective:
Traumatic injury to the eye, a site that displays immune privilege, can lead to the release of previously sequestered antigens that T cells recognize as foreign. This can lead to sight-threatening inflammation in both the injured and uninjured eye.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Item 33 of 40
Question Id: 1763

A 3-year-old boy is being evaluated for persistent diarrhea. Although the patient seemed healthy at his 12-month well child visit, since then he has experienced 4 episodes of otitis media and 3 episodes of pneumococcal pneumonia. He was at the 50th percentile for weight and height at 12 months but is now at the 25th percentile for height and 10th percentile for weight. The patient is referred for upper gastrointestinal endoscopy, and *Giardia lamblia* is isolated from duodenal aspirates. Further workup shows very low serum levels of all immunoglobulin types. Flow cytometry of this patient's peripheral blood is most likely to show a near absence of cells bearing which of the following markers?

○ A. CD4

○ B. CD8

○ C. CD15

○ D. CD16

○ E. CD19

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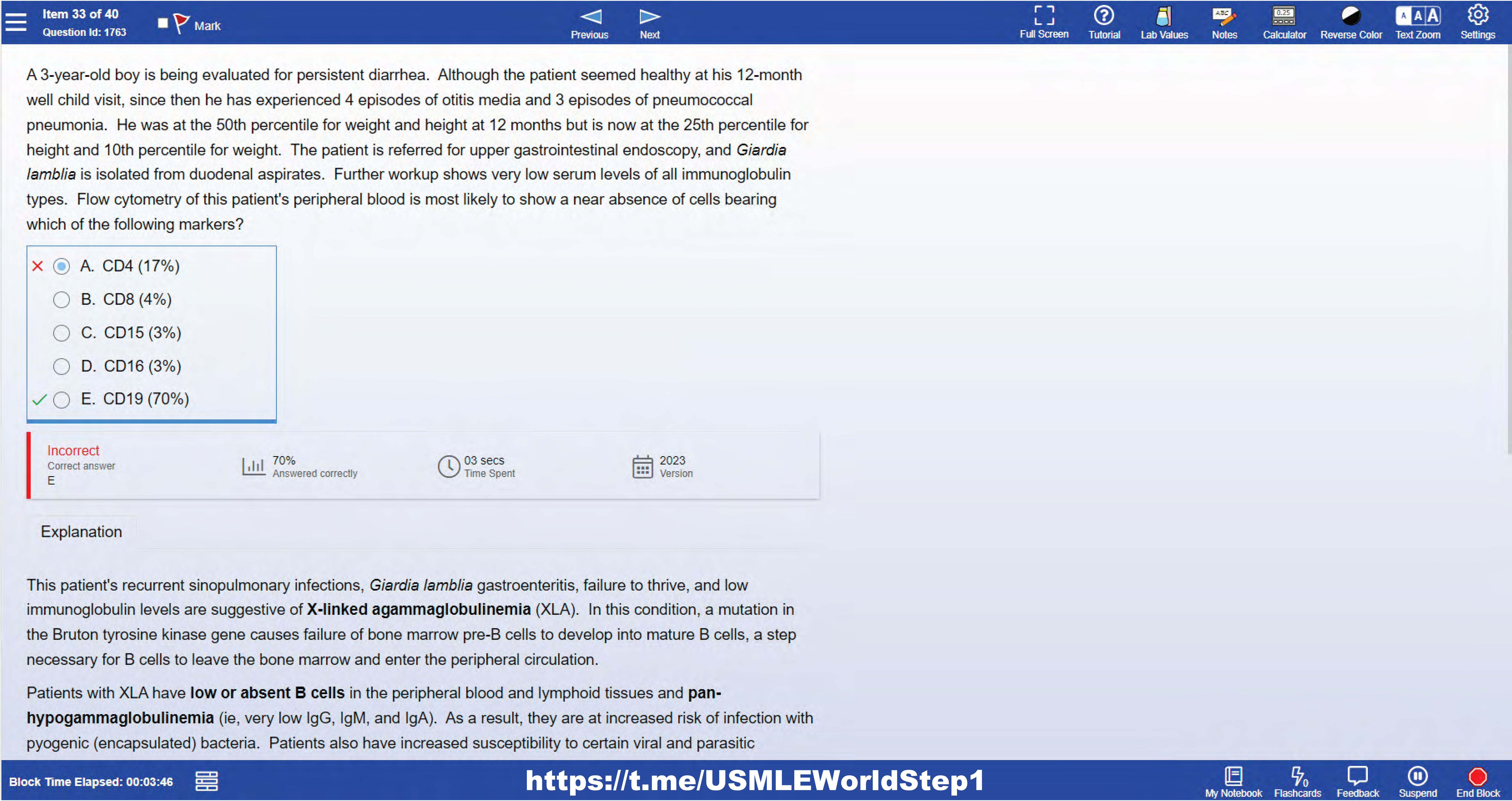
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✗ ● A. CD4 (17%)

○ B. CD8 (4%)

○ C. CD15 (3%)

○ D. CD16 (3%)

✓ ○ E. CD19 (70%)

Incorrect
Correct answer
E

70%
Answered correctly

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Explanation

This patient's recurrent sinopulmonary infections, *Giardia lamblia* gastroenteritis, failure to thrive, and low immunoglobulin levels are suggestive of **X-linked agammaglobulinemia** (XLA). In this condition, a mutation in the Bruton tyrosine kinase gene causes failure of bone marrow pre-B cells to develop into mature B cells, a step necessary for B cells to leave the bone marrow and enter the peripheral circulation.

Patients with XLA have **low or absent B cells** in the peripheral blood and lymphoid tissues and **pan-hypogammaglobulinemia** (ie, very low IgG, IgM, and IgA). As a result, they are at increased risk of infection with pyogenic (encapsulated) bacteria. Patients also have increased susceptibility to certain viral and parasitic

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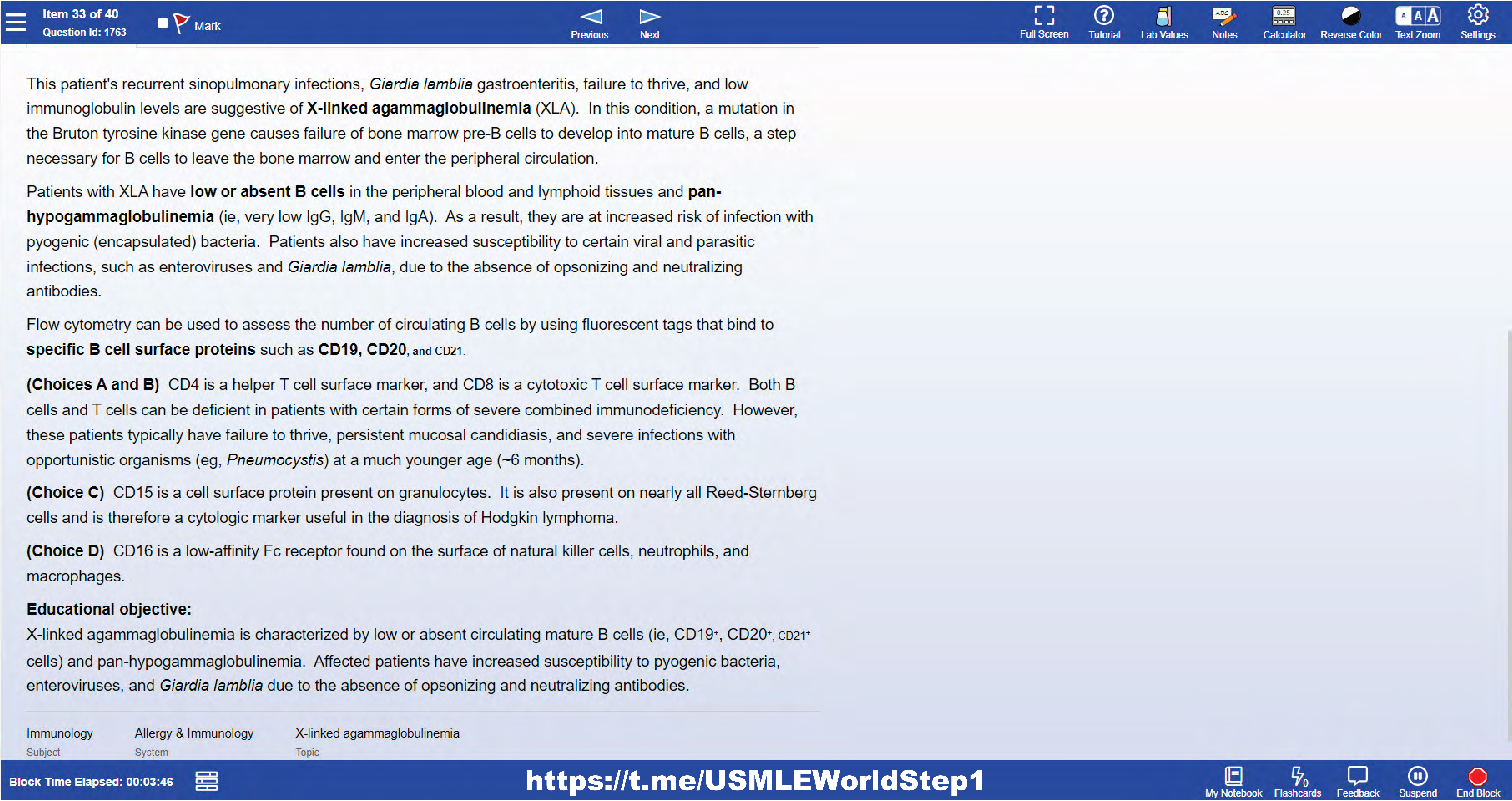

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Patients with XLA have **low or absent B cells** in the peripheral blood and lymphoid tissues and **pan-hypogammaglobulinemia** (ie, very low IgG, IgM, and IgA). As a result, they are at increased risk of infection with pyogenic (encapsulated) bacteria. Patients also have increased susceptibility to certain viral and parasitic infections, such as enteroviruses and *Giardia lamblia*, due to the absence of opsonizing and neutralizing antibodies.

Flow cytometry can be used to assess the number of circulating B cells by using fluorescent tags that bind to **specific B cell surface proteins** such as **CD19, CD20**, **and** CD21.

(Choices A and B) CD4 is a helper T cell surface marker, and CD8 is a cytotoxic T cell surface marker. Both B cells and T cells can be deficient in patients with certain forms of severe combined immunodeficiency. However, these patients typically have failure to thrive, persistent mucosal candidiasis, and severe infections with opportunistic organisms (eg, *Pneumocystis*) at a much younger age (~6 months).

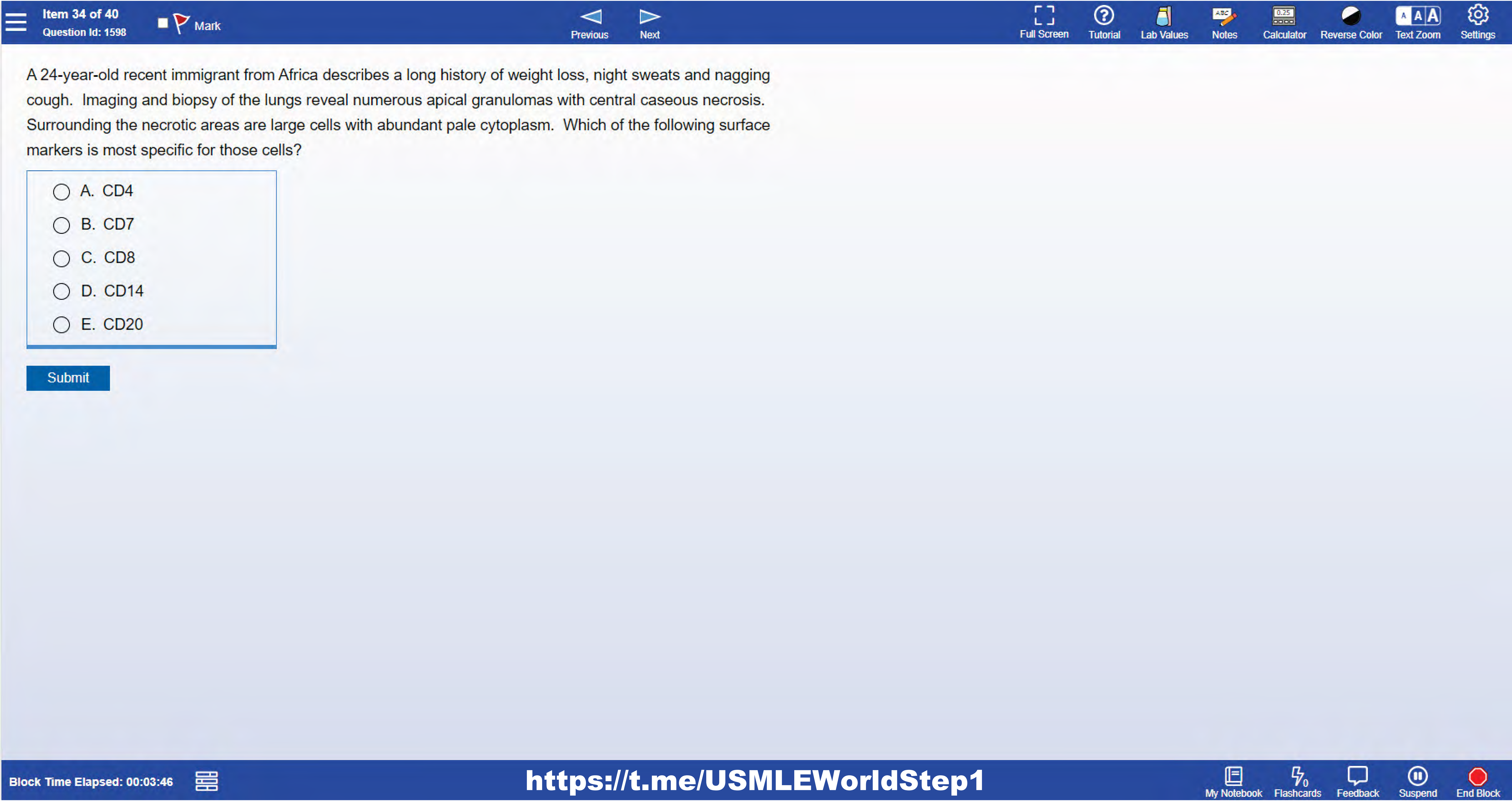
(Choice C) CD15 is a cell surface protein present on granulocytes. It is also present on nearly all Reed-Sternberg cells and is therefore a cytologic marker useful in the diagnosis of Hodgkin lymphoma.

(Choice D) CD16 is a low-affinity Fc receptor found on the surface of natural killer cells, neutrophils, and macrophages.

Educational objective:

X-linked agammaglobulinemia is characterized by low or absent circulating mature B cells (ie, CD19$^+$, CD20$^+$, CD21$^+$ cells) and pan-hypogammaglobulinemia. Affected patients have increased susceptibility to pyogenic bacteria, enteroviruses, and *Giardia lamblia* due to the absence of opsonizing and neutralizing antibodies.

Immunology	Allergy & Immunology	X-linked agammaglobulinemia
Subject	System	Topic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A 24-year-old recent immigrant from Africa describes a long history of weight loss, night sweats and nagging cough. Imaging and biopsy of the lungs reveal numerous apical granulomas with central caseous necrosis. Surrounding the necrotic areas are large cells with abundant pale cytoplasm. Which of the following surface markers is most specific for those cells?

○ A. CD4
○ B. CD7
○ C. CD8
○ D. CD14
○ E. CD20

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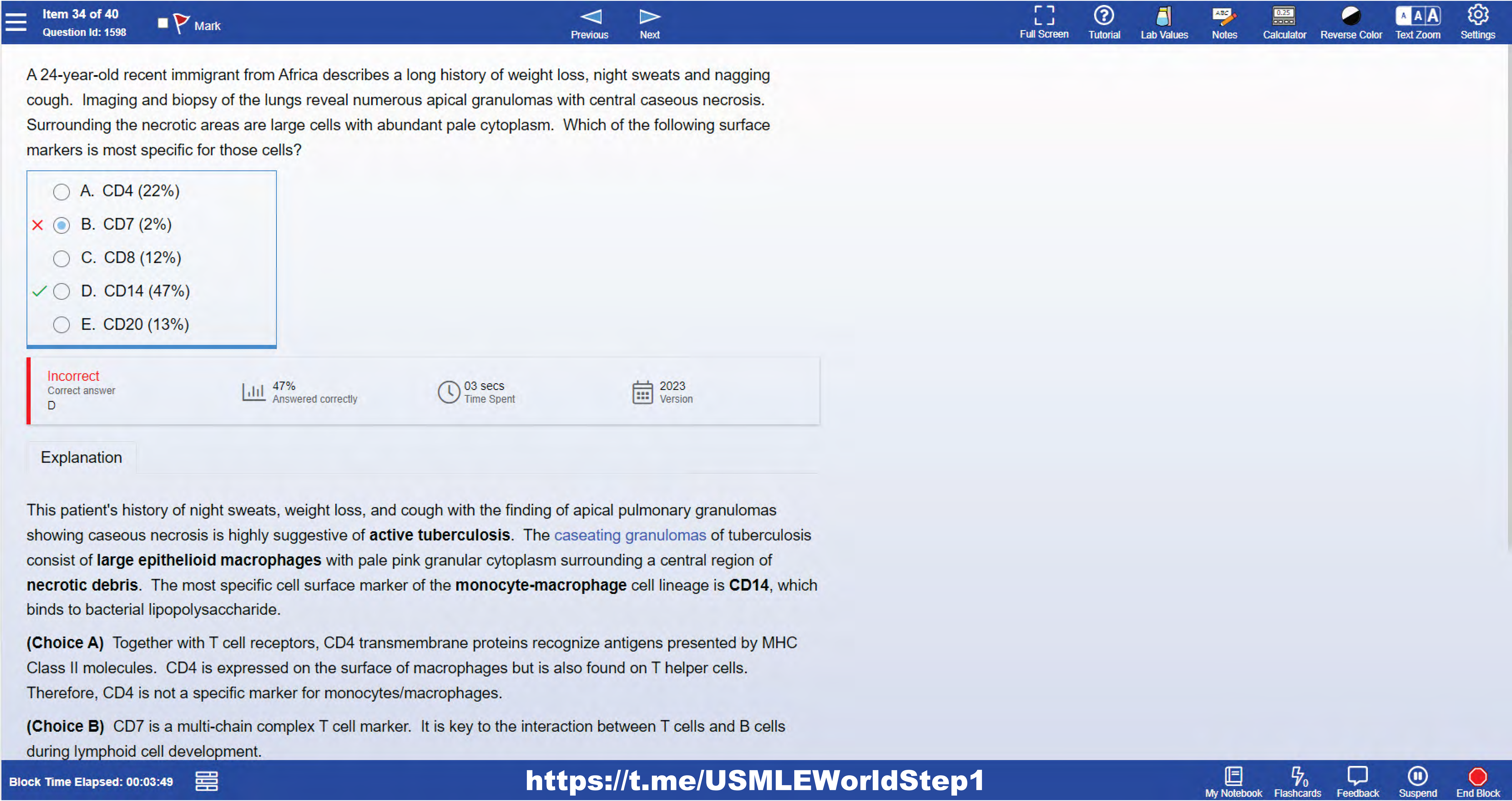
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A 24-year-old recent immigrant from Africa describes a long history of weight loss, night sweats and nagging cough. Imaging and biopsy of the lungs reveal numerous apical granulomas with central caseous necrosis. Surrounding the necrotic areas are large cells with abundant pale cytoplasm. Which of the following surface markers is most specific for those cells?

- ○ A. CD4 (22%)
- ✗ ● B. CD7 (2%)
- ○ C. CD8 (12%)
- ✓ ○ D. CD14 (47%)
- ○ E. CD20 (13%)

Incorrect
Correct answer
D

47%
Answered correctly

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Explanation

This patient's history of night sweats, weight loss, and cough with the finding of apical pulmonary granulomas showing caseous necrosis is highly suggestive of **active tuberculosis**. The caseating granulomas of tuberculosis consist of **large epithelioid macrophages** with pale pink granular cytoplasm surrounding a central region of **necrotic debris**. The most specific cell surface marker of the **monocyte-macrophage** cell lineage is **CD14**, which binds to bacterial lipopolysaccharide.

(Choice A) Together with T cell receptors, CD4 transmembrane proteins recognize antigens presented by MHC Class II molecules. CD4 is expressed on the surface of macrophages but is also found on T helper cells. Therefore, CD4 is not a specific marker for monocytes/macrophages.

(Choice B) CD7 is a multi-chain complex T cell marker. It is key to the interaction between T cells and B cells during lymphoid cell development.

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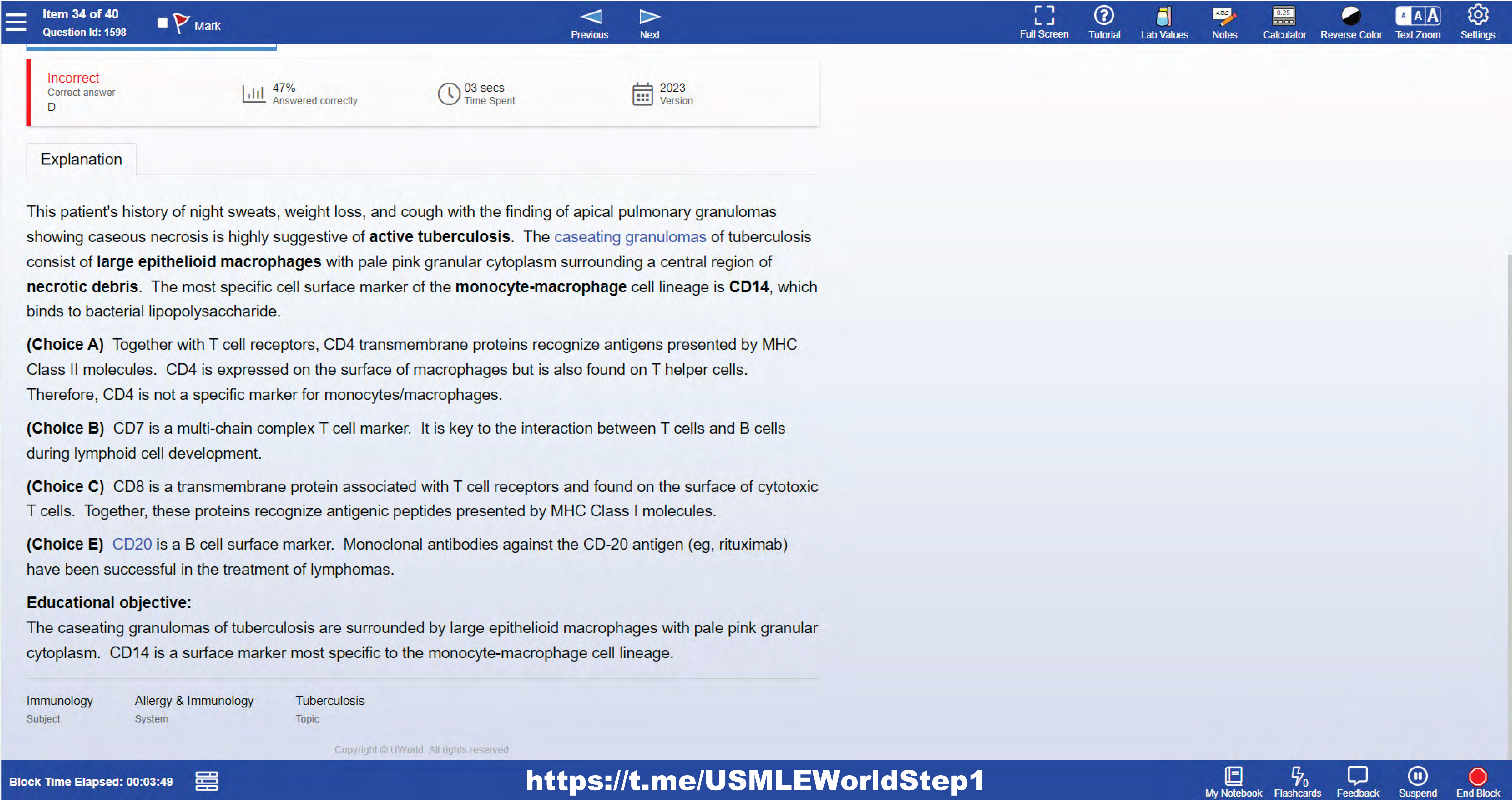

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Correct answer
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47%
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Explanation

This patient's history of night sweats, weight loss, and cough with the finding of apical pulmonary granulomas showing caseous necrosis is highly suggestive of **active tuberculosis**. The caseating granulomas of tuberculosis consist of **large epithelioid macrophages** with pale pink granular cytoplasm surrounding a central region of **necrotic debris**. The most specific cell surface marker of the **monocyte-macrophage** cell lineage is **CD14**, which binds to bacterial lipopolysaccharide.

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(Choice B) CD7 is a multi-chain complex T cell marker. It is key to the interaction between T cells and B cells during lymphoid cell development.

(Choice C) CD8 is a transmembrane protein associated with T cell receptors and found on the surface of cytotoxic T cells. Together, these proteins recognize antigenic peptides presented by MHC Class I molecules.

(Choice E) CD20 is a B cell surface marker. Monoclonal antibodies against the CD-20 antigen (eg, rituximab) have been successful in the treatment of lymphomas.

Educational objective:
The caseating granulomas of tuberculosis are surrounded by large epithelioid macrophages with pale pink granular cytoplasm. CD14 is a surface marker most specific to the monocyte-macrophage cell lineage.

Immunology	Allergy & Immunology	Tuberculosis
Subject	System	Topic

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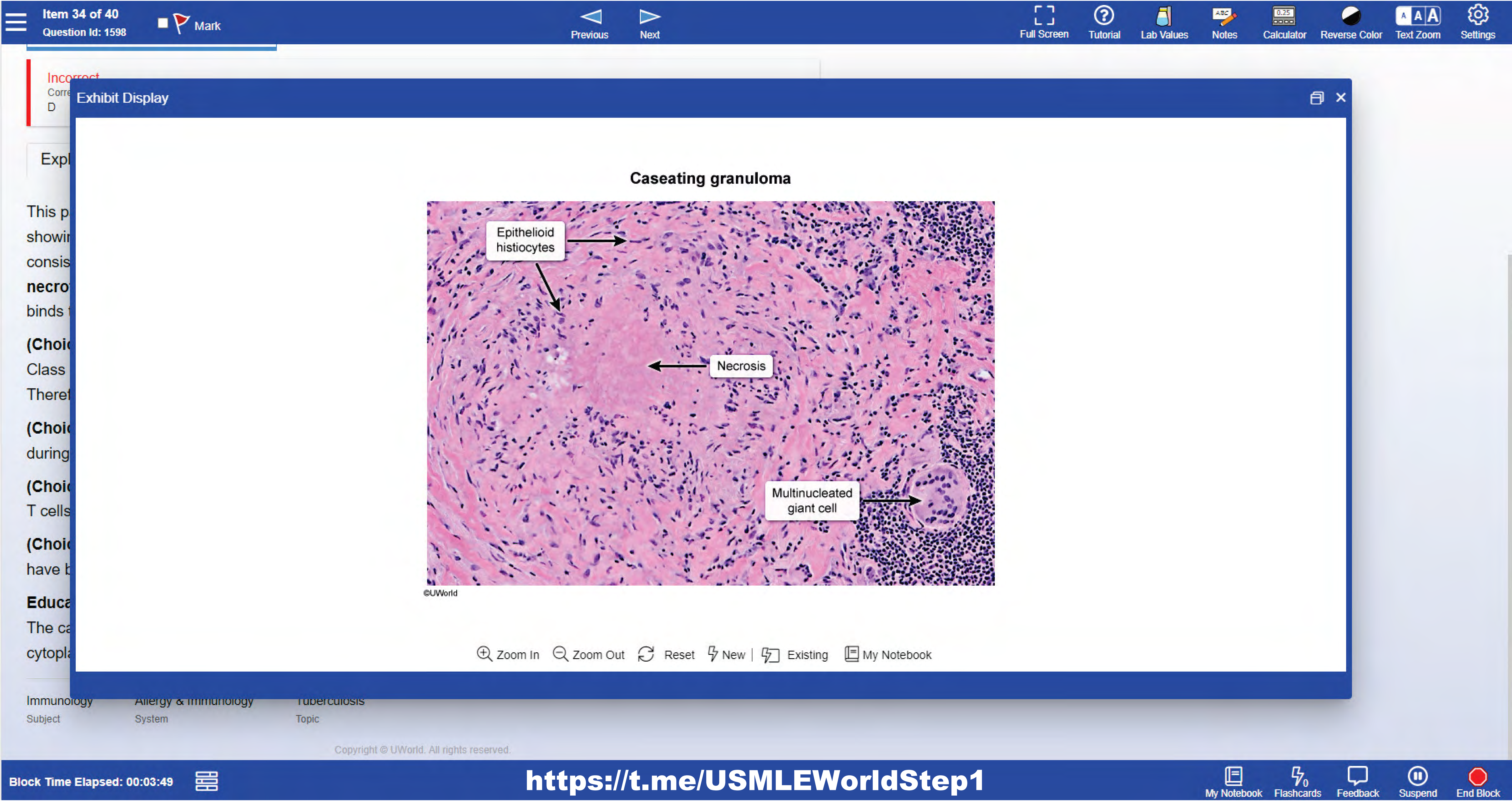
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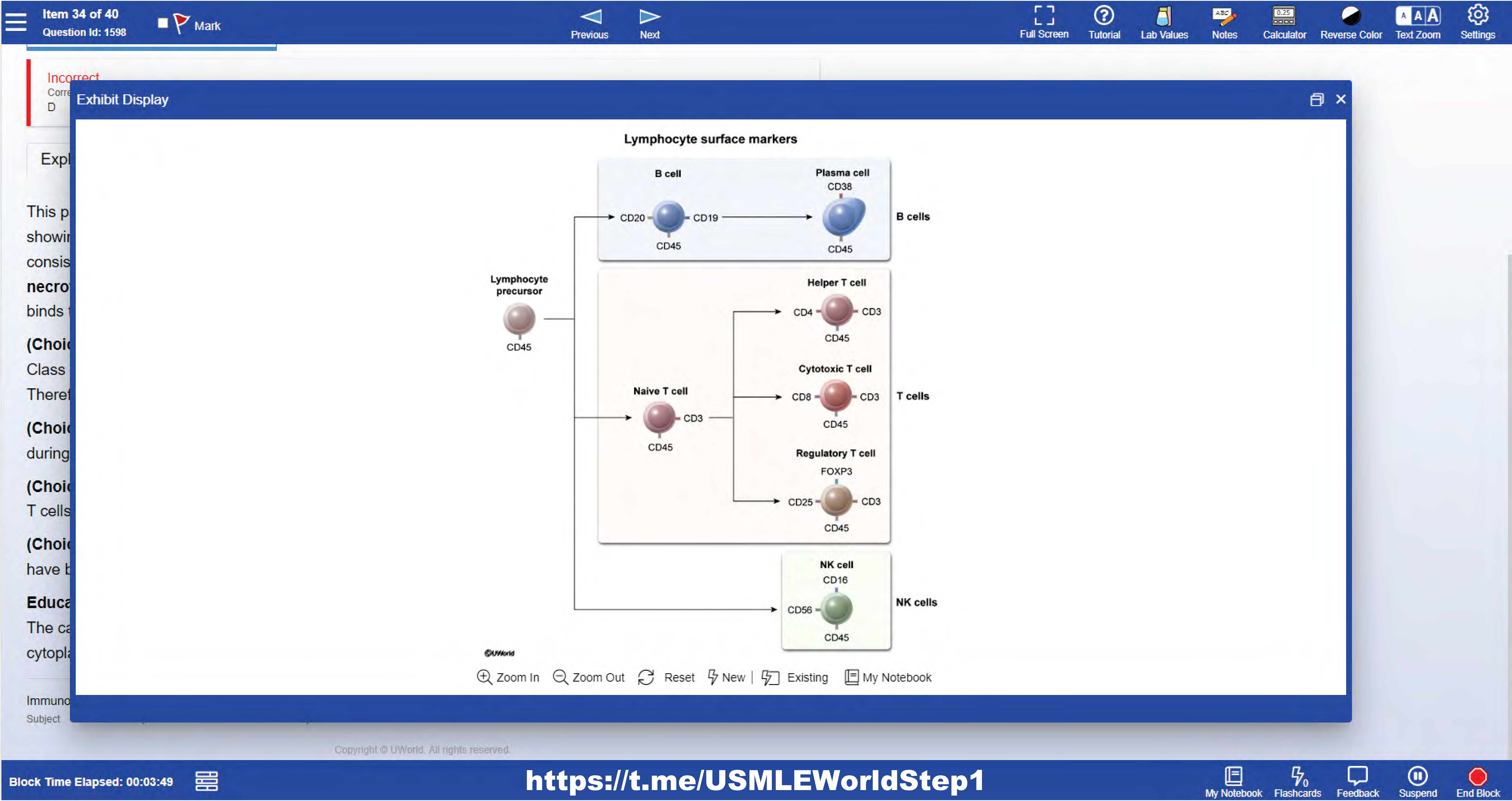
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Exhibit Display

Lymphocyte surface markers

B cell
CD20
CD19
CD45
Plasma cell
CD38
CD45
B cells
Lymphocyte precursor
CD45
Helper T cell
CD4
CD3
CD45
Cytotoxic T cell
CD8
CD3
CD45
Naive T cell
CD3
CD45
T cells
Regulatory T cell
FOXP3
CD25
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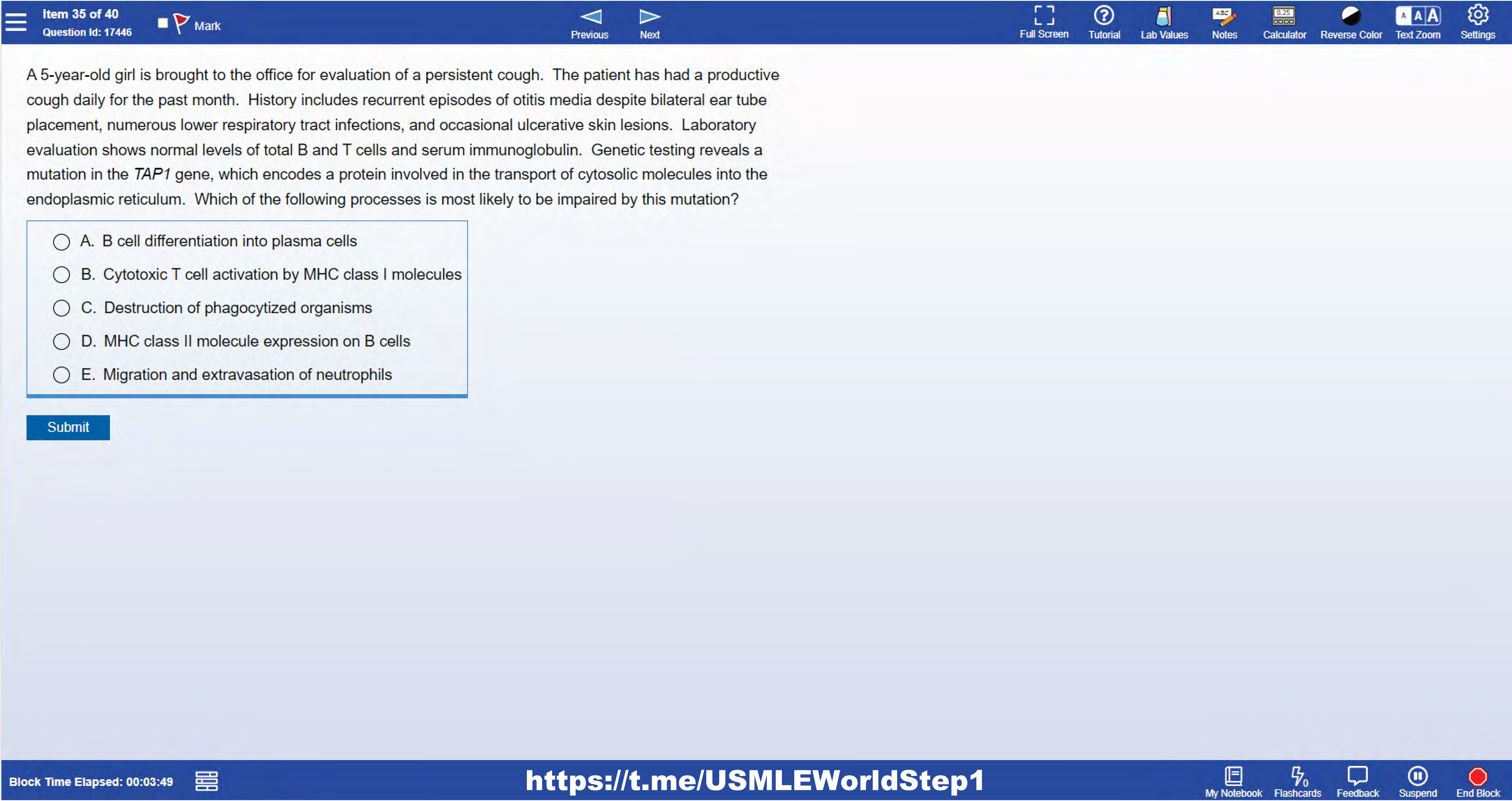
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Question Id: 17446

A 5-year-old girl is brought to the office for evaluation of a persistent cough. The patient has had a productive cough daily for the past month. History includes recurrent episodes of otitis media despite bilateral ear tube placement, numerous lower respiratory tract infections, and occasional ulcerative skin lesions. Laboratory evaluation shows normal levels of total B and T cells and serum immunoglobulin. Genetic testing reveals a mutation in the *TAP1* gene, which encodes a protein involved in the transport of cytosolic molecules into the endoplasmic reticulum. Which of the following processes is most likely to be impaired by this mutation?

○ A. B cell differentiation into plasma cells
○ B. Cytotoxic T cell activation by MHC class I molecules
○ C. Destruction of phagocytized organisms
○ D. MHC class II molecule expression on B cells
○ E. Migration and extravasation of neutrophils

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○ A. B cell differentiation into plasma cells (4%)

✓ ○ B. Cytotoxic T cell activation by MHC class I molecules (43%)

✗ ● C. Destruction of phagocytized organisms (16%)

○ D. MHC class II molecule expression on B cells (26%)

○ E. Migration and extravasation of neutrophils (8%)

Incorrect
Correct answer
B

43%
Answered correctly

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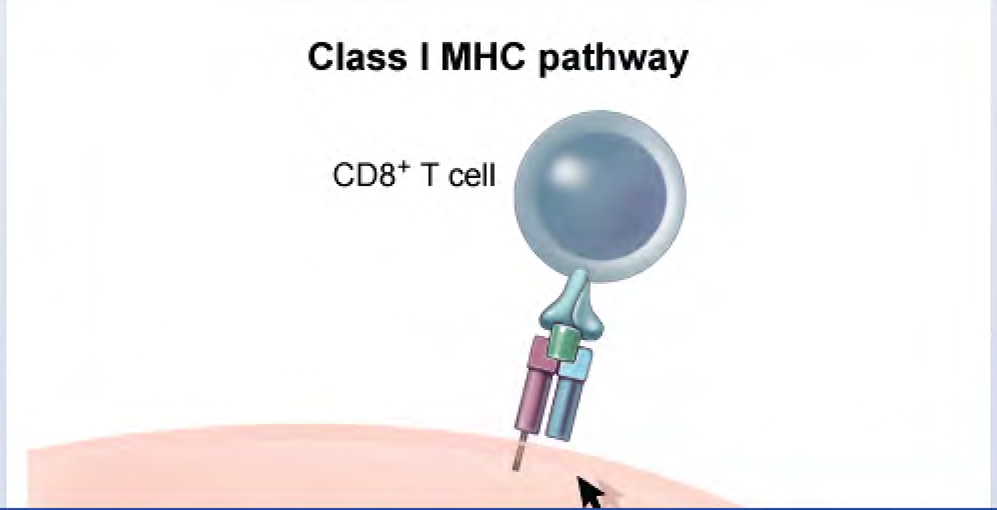
Explanation



Class I MHC pathway

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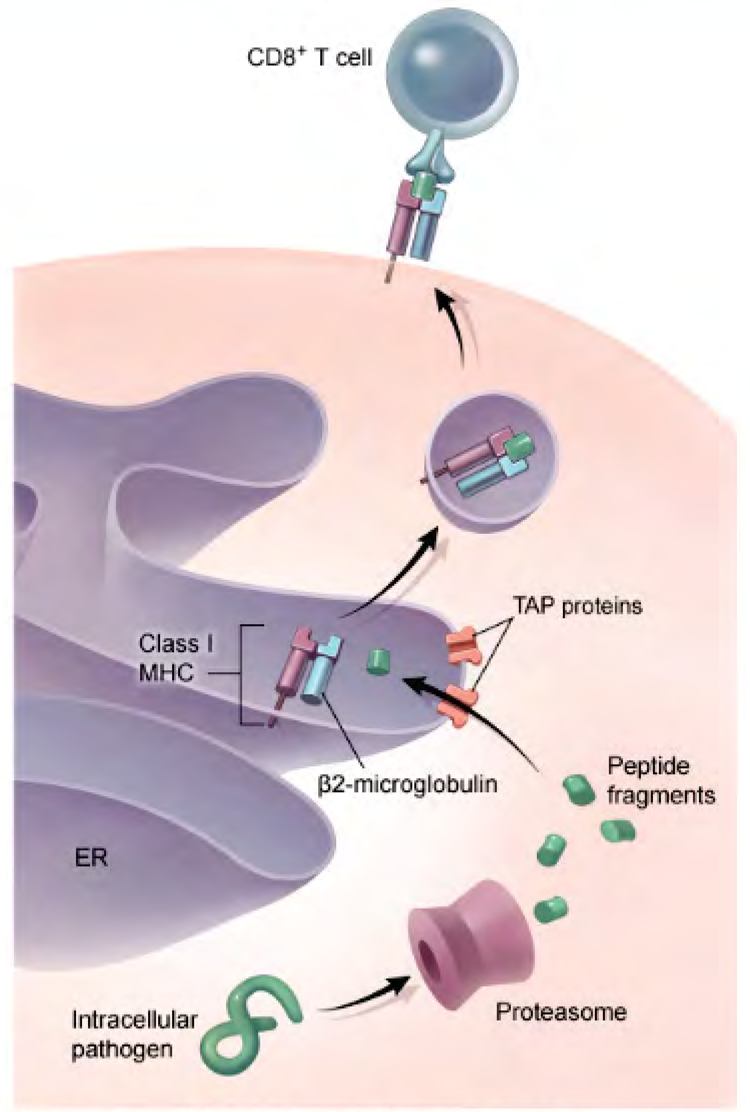
Class I MHC pathway


CD8⁺ T cell
TAP proteins
Class I MHC
β2-microglobulin
Peptide fragments
ER
Intracellular pathogen
Proteasome

ER = endoplasmic reticulum; **MHC** = major histocompatibility complex;
TAP = transporter associated with antigen processing.

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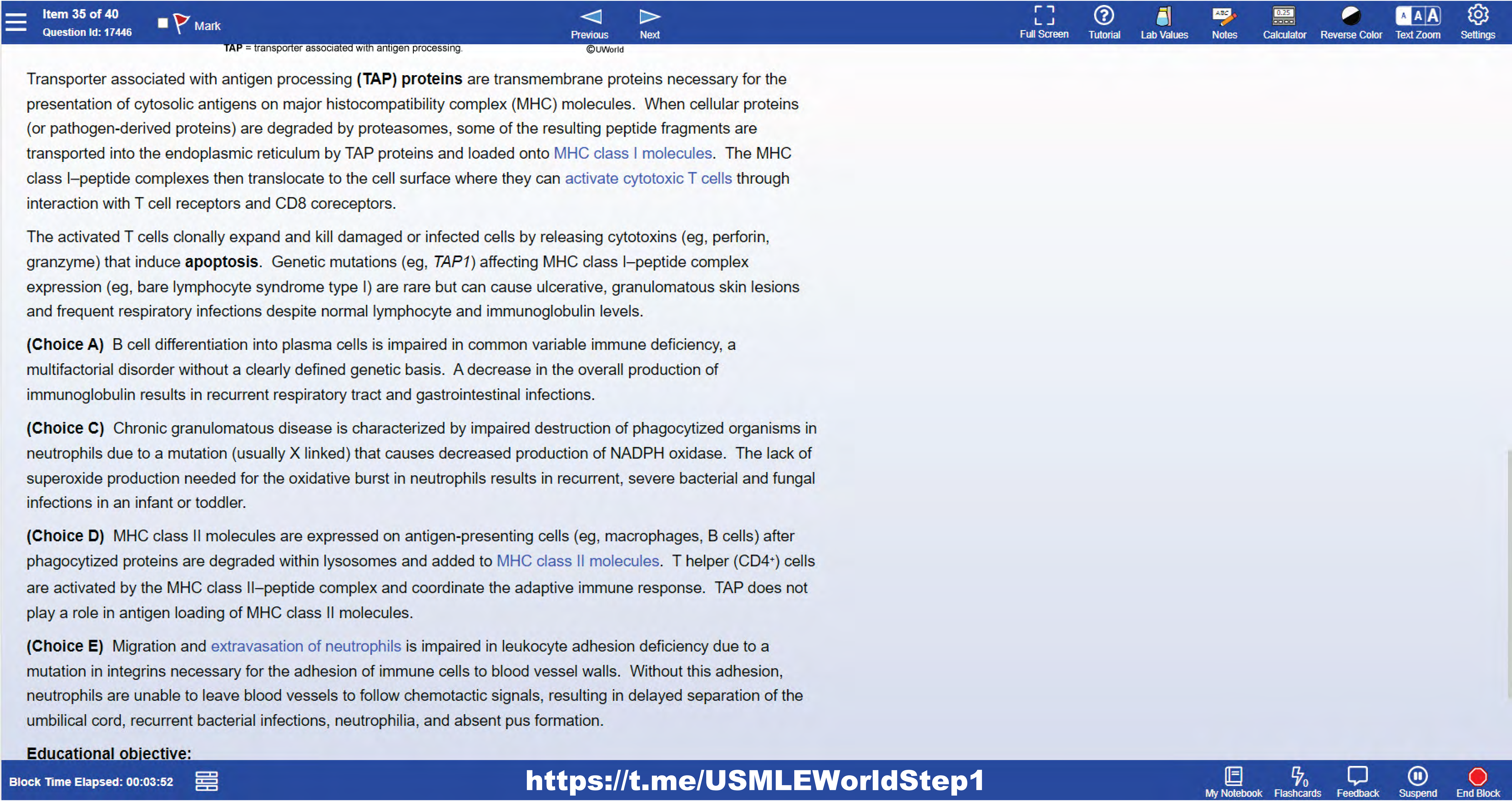

TAP = transporter associated with antigen processing.

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Transporter associated with antigen processing **(TAP) proteins** are transmembrane proteins necessary for the presentation of cytosolic antigens on major histocompatibility complex (MHC) molecules. When cellular proteins (or pathogen-derived proteins) are degraded by proteasomes, some of the resulting peptide fragments are transported into the endoplasmic reticulum by TAP proteins and loaded onto MHC class I molecules. The MHC class I–peptide complexes then translocate to the cell surface where they can activate cytotoxic T cells through interaction with T cell receptors and CD8 coreceptors.

The activated T cells clonally expand and kill damaged or infected cells by releasing cytotoxins (eg, perforin, granzyme) that induce **apoptosis**. Genetic mutations (eg, *TAP1*) affecting MHC class I–peptide complex expression (eg, bare lymphocyte syndrome type I) are rare but can cause ulcerative, granulomatous skin lesions and frequent respiratory infections despite normal lymphocyte and immunoglobulin levels.

(Choice A) B cell differentiation into plasma cells is impaired in common variable immune deficiency, a multifactorial disorder without a clearly defined genetic basis. A decrease in the overall production of immunoglobulin results in recurrent respiratory tract and gastrointestinal infections.

(Choice C) Chronic granulomatous disease is characterized by impaired destruction of phagocytized organisms in neutrophils due to a mutation (usually X linked) that causes decreased production of NADPH oxidase. The lack of superoxide production needed for the oxidative burst in neutrophils results in recurrent, severe bacterial and fungal infections in an infant or toddler.

(Choice D) MHC class II molecules are expressed on antigen-presenting cells (eg, macrophages, B cells) after phagocytized proteins are degraded within lysosomes and added to MHC class II molecules. T helper ($CD4^+$) cells are activated by the MHC class II–peptide complex and coordinate the adaptive immune response. TAP does not play a role in antigen loading of MHC class II molecules.

(Choice E) Migration and extravasation of neutrophils is impaired in leukocyte adhesion deficiency due to a mutation in integrins necessary for the adhesion of immune cells to blood vessel walls. Without this adhesion, neutrophils are unable to leave blood vessels to follow chemotactic signals, resulting in delayed separation of the umbilical cord, recurrent bacterial infections, neutrophilia, and absent pus formation.

Educational objective:

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(or pathogen-derived proteins) are degraded by proteasomes, some of the resulting peptide fragments are transported into the endoplasmic reticulum by TAP proteins and loaded onto MHC class I molecules. The MHC class I–peptide complexes then translocate to the cell surface where they can activate cytotoxic T cells through interaction with T cell receptors and CD8 coreceptors.

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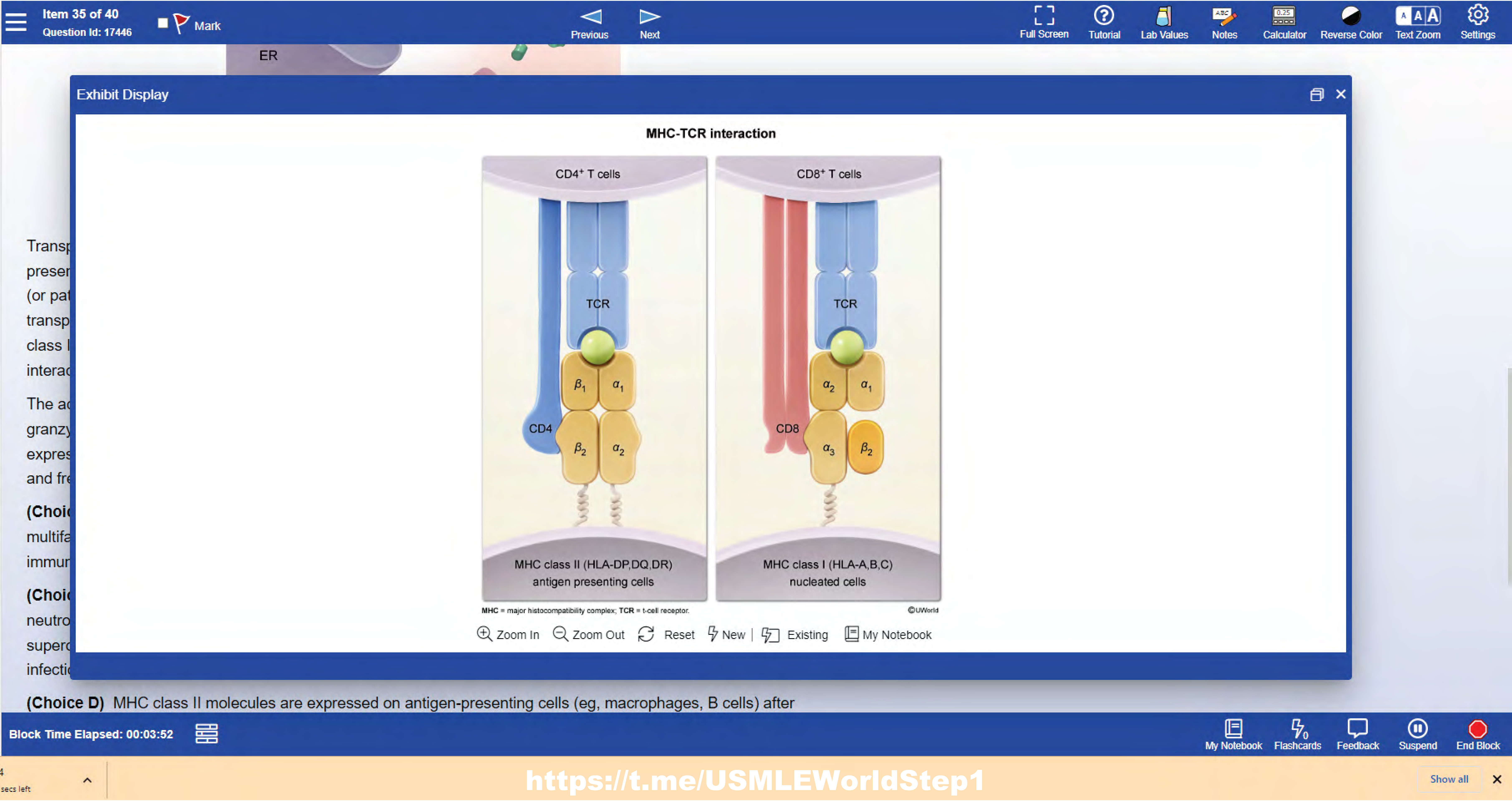
(Choice C) Chronic granulomatous disease is characterized by impaired destruction of phagocytized organisms in neutrophils due to a mutation (usually X linked) that causes decreased production of NADPH oxidase. The lack of superoxide production needed for the oxidative burst in neutrophils results in recurrent, severe bacterial and fungal infections in an infant or toddler.

(Choice D) MHC class II molecules are expressed on antigen-presenting cells (eg, macrophages, B cells) after phagocytized proteins are degraded within lysosomes and added to MHC class II molecules. T helper ($CD4^+$) cells are activated by the MHC class II–peptide complex and coordinate the adaptive immune response. TAP does not play a role in antigen loading of MHC class II molecules.

(Choice E) Migration and extravasation of neutrophils is impaired in leukocyte adhesion deficiency due to a mutation in integrins necessary for the adhesion of immune cells to blood vessel walls. Without this adhesion, neutrophils are unable to leave blood vessels to follow chemotactic signals, resulting in delayed separation of the umbilical cord, recurrent bacterial infections, neutrophilia, and absent pus formation.

Educational objective:

Transporter associated with antigen processing (TAP) proteins are necessary for loading of cytoplasmic (eg, viral) proteins onto major histocompatibility complex (MHC) class I molecules. The MHC class I–peptide complex can then activate $CD8^+$ cytotoxic T cells through interaction with the T cell receptor and CD8 coreceptor.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CD8⁺ T cells
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MHC-TCR interaction

MHC class II (HLA-DP,DQ,DR)
antigen presenting cells

MHC class I (HLA-A,B,C)
nucleated cells

MHC = major histocompatibility complex; **TCR** = t-cell receptor.

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(Choice D) MHC class II molecules are expressed on antigen-presenting cells (eg, macrophages, B cells) after

TAP = transporter associated with antigen processing. ©UWorld

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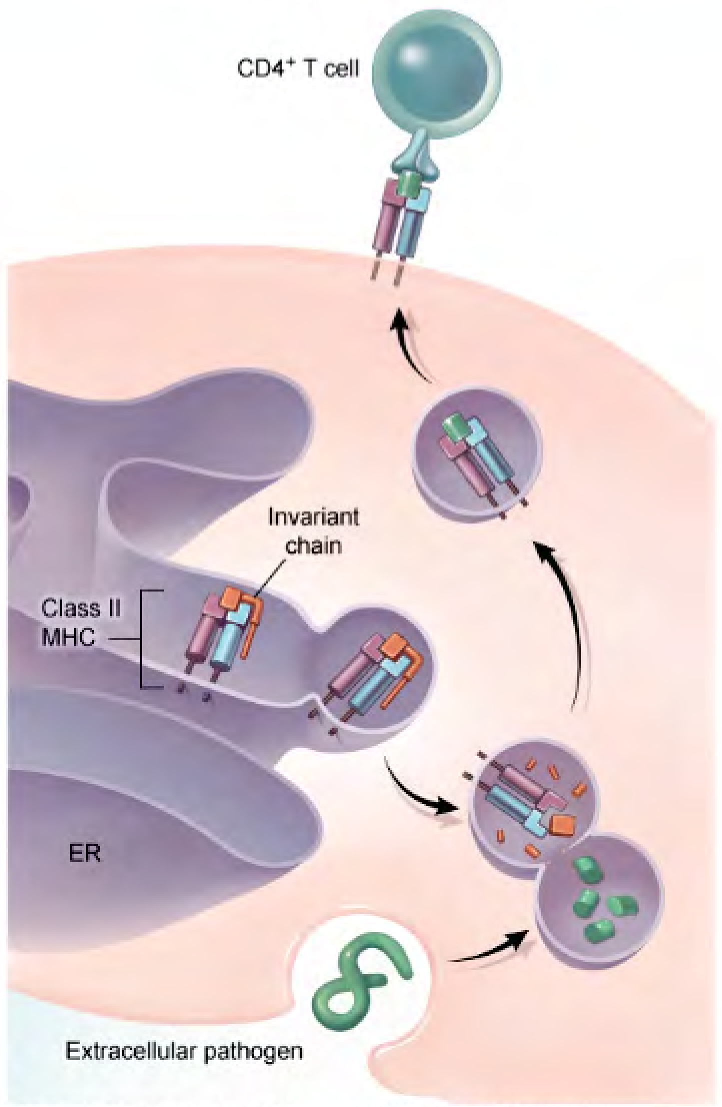
Class II MHC pathway


CD4⁺ T cell
Invariant chain
Class II MHC
ER
Extracellular pathogen

ER = endoplasmic reticulum; **MHC** = major histocompatibility complex. ©UWorld

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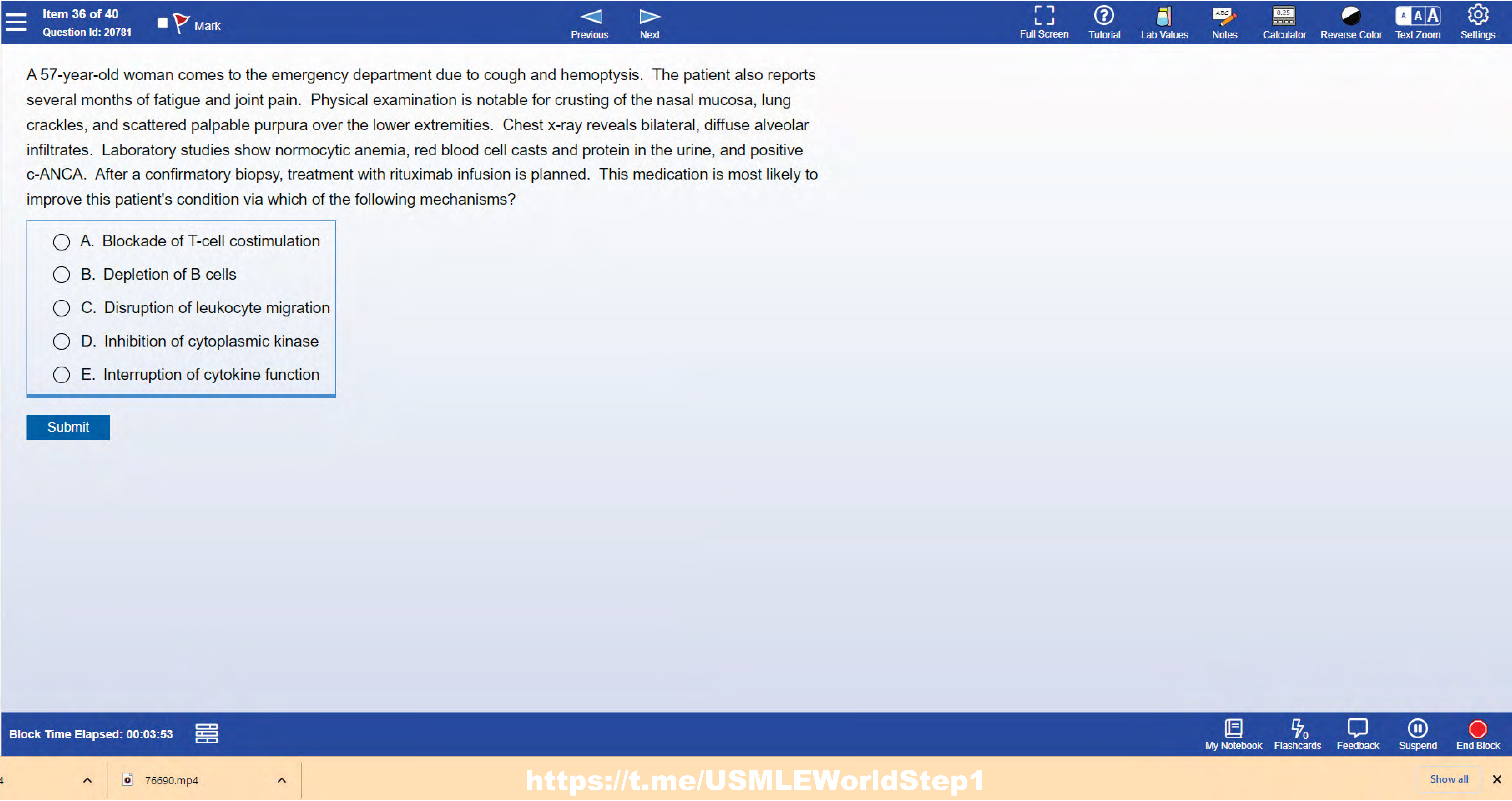
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Item 36 of 40
Question Id: 20781

A 57-year-old woman comes to the emergency department due to cough and hemoptysis. The patient also reports several months of fatigue and joint pain. Physical examination is notable for crusting of the nasal mucosa, lung crackles, and scattered palpable purpura over the lower extremities. Chest x-ray reveals bilateral, diffuse alveolar infiltrates. Laboratory studies show normocytic anemia, red blood cell casts and protein in the urine, and positive c-ANCA. After a confirmatory biopsy, treatment with rituximab infusion is planned. This medication is most likely to improve this patient's condition via which of the following mechanisms?

○ A. Blockade of T-cell costimulation
○ B. Depletion of B cells
○ C. Disruption of leukocyte migration
○ D. Inhibition of cytoplasmic kinase
○ E. Interruption of cytokine function

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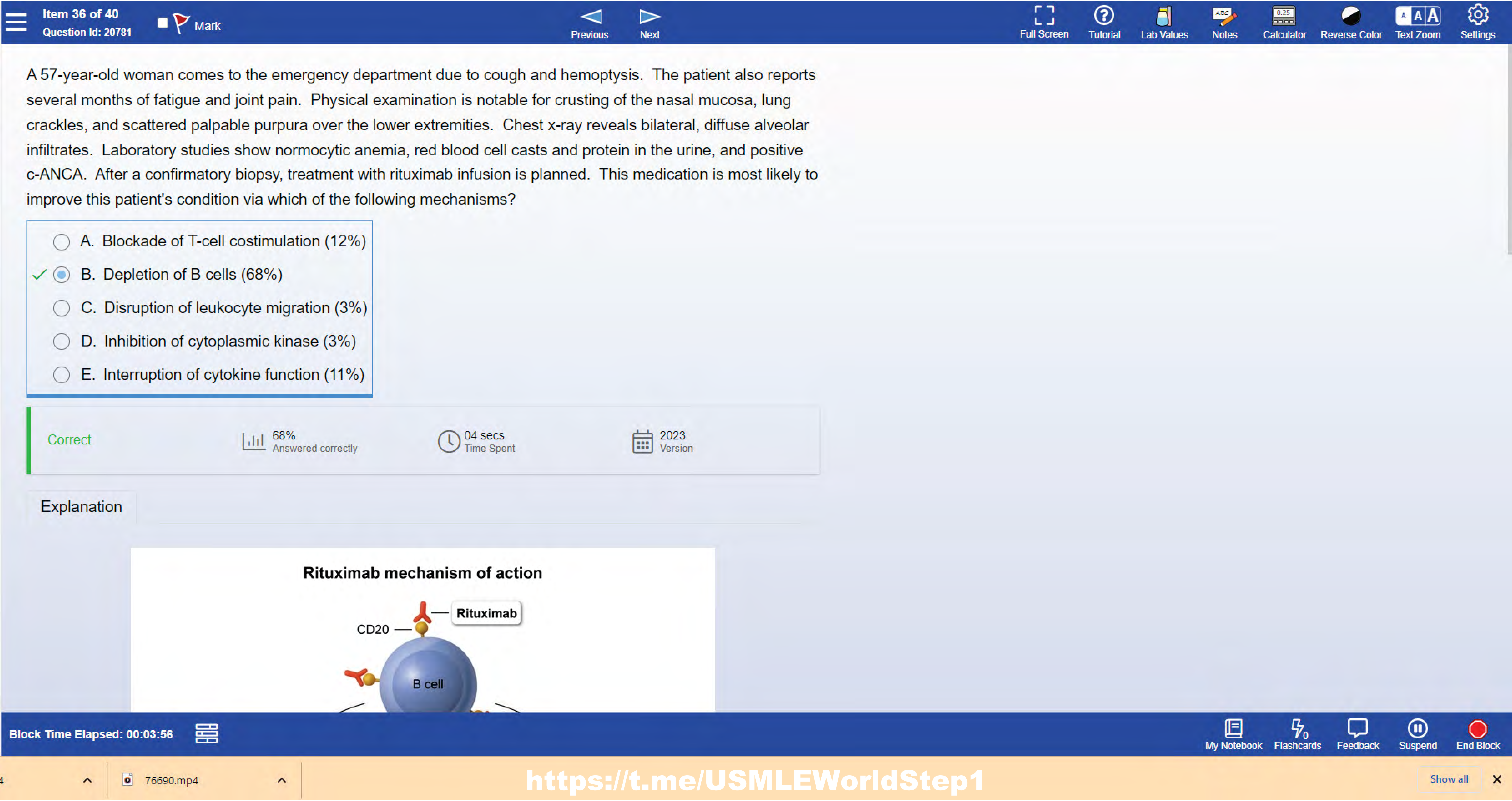
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- ○ A. Blockade of T-cell costimulation (12%)
- ✓ ● B. Depletion of B cells (68%)
- ○ C. Disruption of leukocyte migration (3%)
- ○ D. Inhibition of cytoplasmic kinase (3%)
- ○ E. Interruption of cytokine function (11%)

Correct

68% Answered correctly

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Explanation

Rituximab mechanism of action

Rituximab
CD20
B cell
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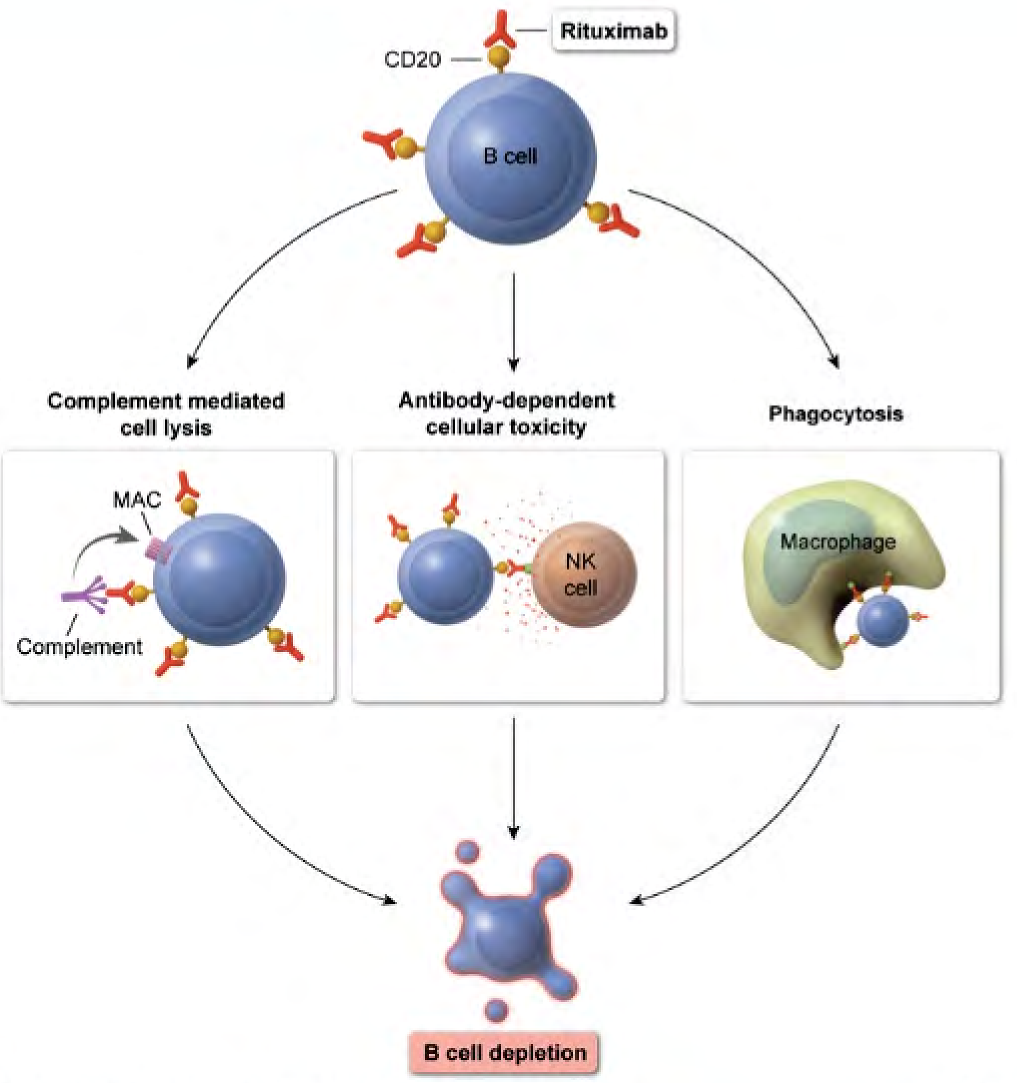
Rituximab mechanism of action


Rituximab
CD20
B cell
Complement mediated cell lysis
Antibody-dependent cellular toxicity
Phagocytosis
MAC
Complement
NK cell
Macrophage
B cell depletion

MAC = membrane attack complex; **NK cell** = natural killer cell.

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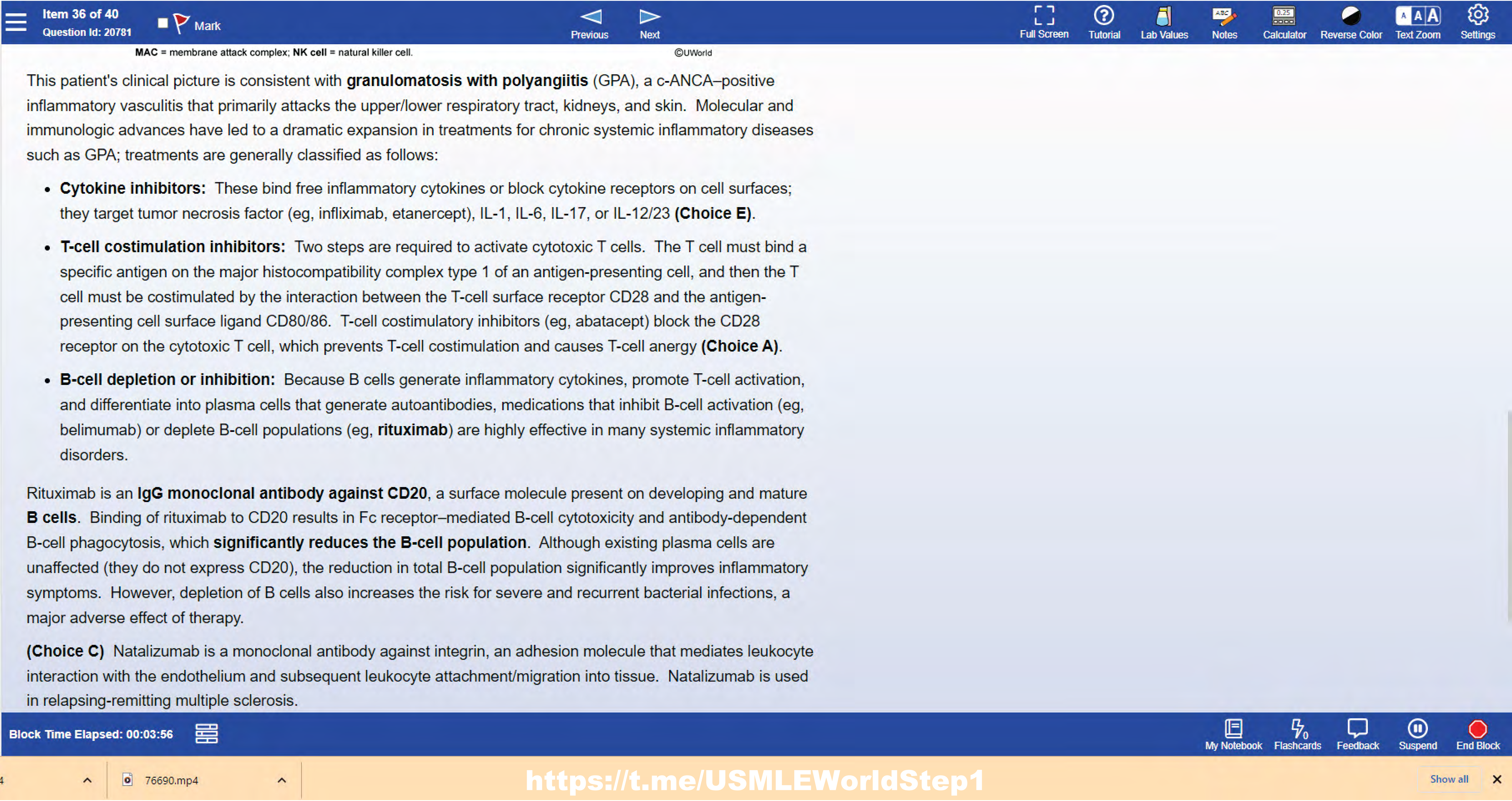

MAC = membrane attack complex; **NK cell** = natural killer cell.

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This patient's clinical picture is consistent with **granulomatosis with polyangiitis** (GPA), a c-ANCA–positive inflammatory vasculitis that primarily attacks the upper/lower respiratory tract, kidneys, and skin. Molecular and immunologic advances have led to a dramatic expansion in treatments for chronic systemic inflammatory diseases such as GPA; treatments are generally classified as follows:

- **Cytokine inhibitors:** These bind free inflammatory cytokines or block cytokine receptors on cell surfaces; they target tumor necrosis factor (eg, infliximab, etanercept), IL-1, IL-6, IL-17, or IL-12/23 **(Choice E)**.
- **T-cell costimulation inhibitors:** Two steps are required to activate cytotoxic T cells. The T cell must bind a specific antigen on the major histocompatibility complex type 1 of an antigen-presenting cell, and then the T cell must be costimulated by the interaction between the T-cell surface receptor CD28 and the antigen-presenting cell surface ligand CD80/86. T-cell costimulatory inhibitors (eg, abatacept) block the CD28 receptor on the cytotoxic T cell, which prevents T-cell costimulation and causes T-cell anergy **(Choice A)**.
- **B-cell depletion or inhibition:** Because B cells generate inflammatory cytokines, promote T-cell activation, and differentiate into plasma cells that generate autoantibodies, medications that inhibit B-cell activation (eg, belimumab) or deplete B-cell populations (eg, **rituximab**) are highly effective in many systemic inflammatory disorders.

Rituximab is an **IgG monoclonal antibody against CD20**, a surface molecule present on developing and mature **B cells**. Binding of rituximab to CD20 results in Fc receptor–mediated B-cell cytotoxicity and antibody-dependent B-cell phagocytosis, which **significantly reduces the B-cell population**. Although existing plasma cells are unaffected (they do not express CD20), the reduction in total B-cell population significantly improves inflammatory symptoms. However, depletion of B cells also increases the risk for severe and recurrent bacterial infections, a major adverse effect of therapy.

(Choice C) Natalizumab is a monoclonal antibody against integrin, an adhesion molecule that mediates leukocyte interaction with the endothelium and subsequent leukocyte attachment/migration into tissue. Natalizumab is used in relapsing-remitting multiple sclerosis.

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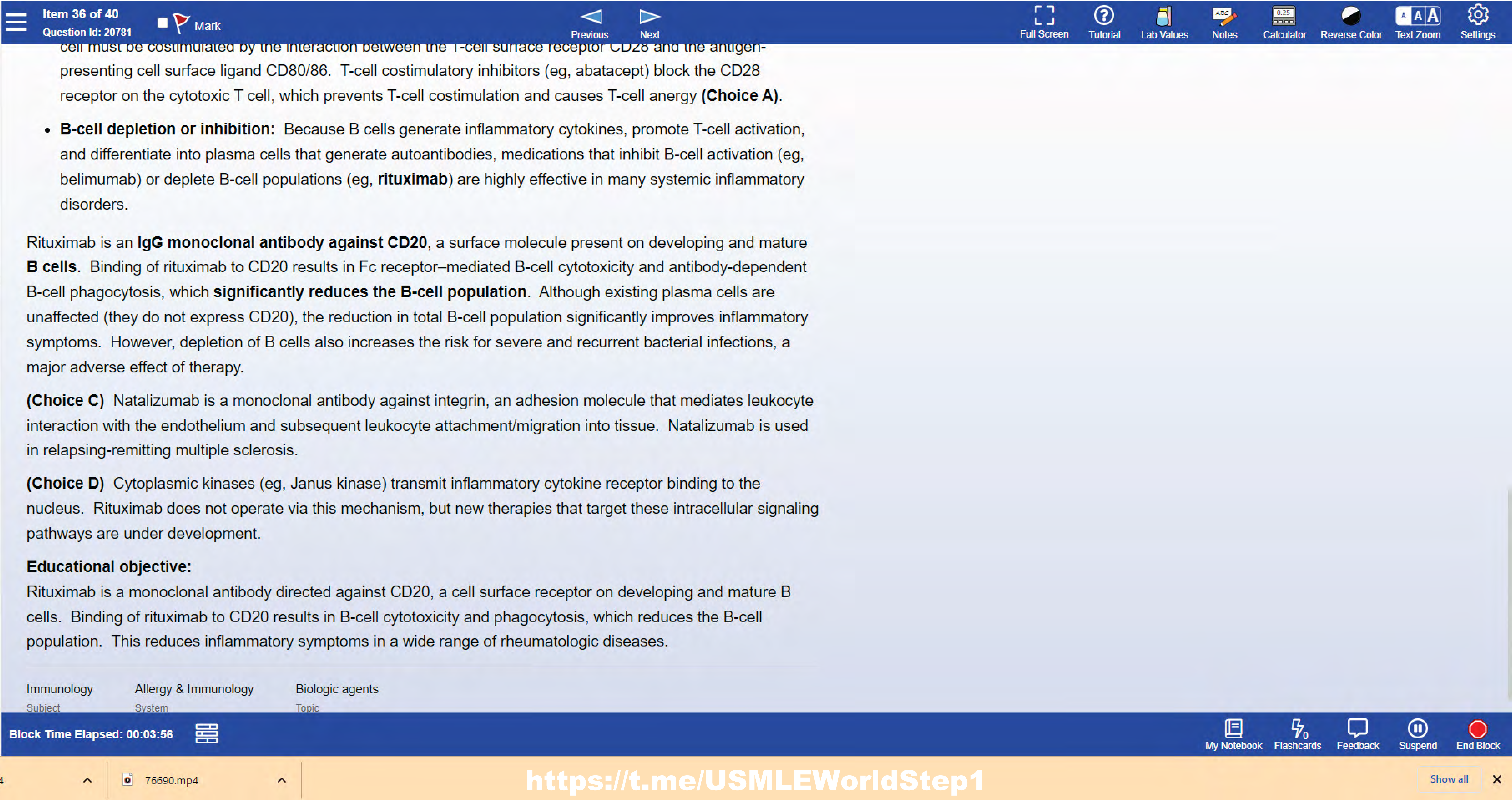

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- **B-cell depletion or inhibition:** Because B cells generate inflammatory cytokines, promote T-cell activation, and differentiate into plasma cells that generate autoantibodies, medications that inhibit B-cell activation (eg, belimumab) or deplete B-cell populations (eg, **rituximab**) are highly effective in many systemic inflammatory disorders.

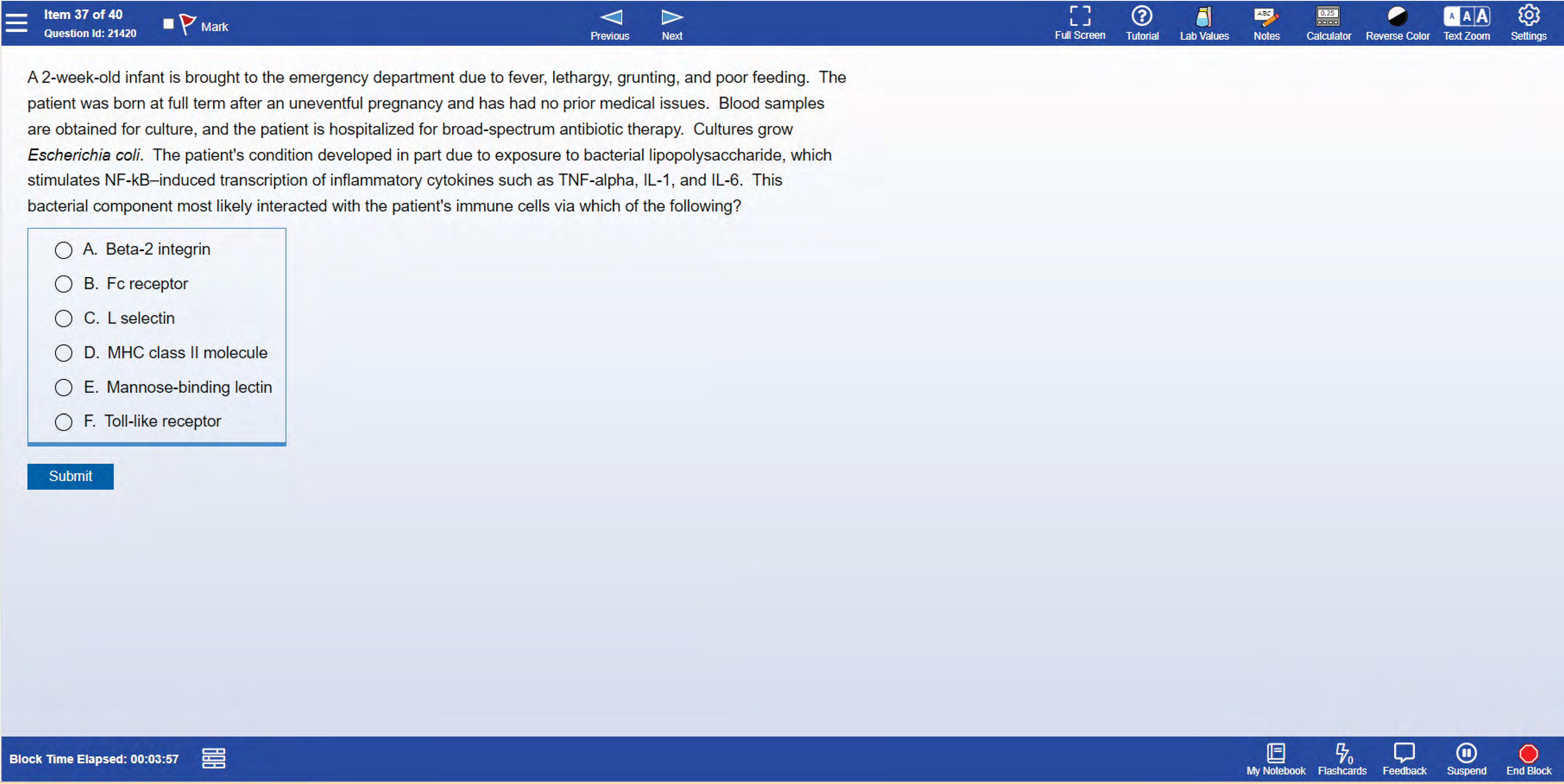
Rituximab is an **IgG monoclonal antibody against CD20**, a surface molecule present on developing and mature **B cells**. Binding of rituximab to CD20 results in Fc receptor–mediated B-cell cytotoxicity and antibody-dependent B-cell phagocytosis, which **significantly reduces the B-cell population**. Although existing plasma cells are unaffected (they do not express CD20), the reduction in total B-cell population significantly improves inflammatory symptoms. However, depletion of B cells also increases the risk for severe and recurrent bacterial infections, a major adverse effect of therapy.

(Choice C) Natalizumab is a monoclonal antibody against integrin, an adhesion molecule that mediates leukocyte interaction with the endothelium and subsequent leukocyte attachment/migration into tissue. Natalizumab is used in relapsing-remitting multiple sclerosis.

(Choice D) Cytoplasmic kinases (eg, Janus kinase) transmit inflammatory cytokine receptor binding to the nucleus. Rituximab does not operate via this mechanism, but new therapies that target these intracellular signaling pathways are under development.

Educational objective:
Rituximab is a monoclonal antibody directed against CD20, a cell surface receptor on developing and mature B cells. Binding of rituximab to CD20 results in B-cell cytotoxicity and phagocytosis, which reduces the B-cell population. This reduces inflammatory symptoms in a wide range of rheumatologic diseases.

Immunology	Allergy & Immunology	Biologic agents
Subject	System	Topic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A 2-week-old infant is brought to the emergency department due to fever, lethargy, grunting, and poor feeding. The patient was born at full term after an uneventful pregnancy and has had no prior medical issues. Blood samples are obtained for culture, and the patient is hospitalized for broad-spectrum antibiotic therapy. Cultures grow *Escherichia coli*. The patient's condition developed in part due to exposure to bacterial lipopolysaccharide, which stimulates NF-kB–induced transcription of inflammatory cytokines such as TNF-alpha, IL-1, and IL-6. This bacterial component most likely interacted with the patient's immune cells via which of the following?

○ A. Beta-2 integrin
○ B. Fc receptor
○ C. L selectin
○ D. MHC class II molecule
○ E. Mannose-binding lectin
○ F. Toll-like receptor

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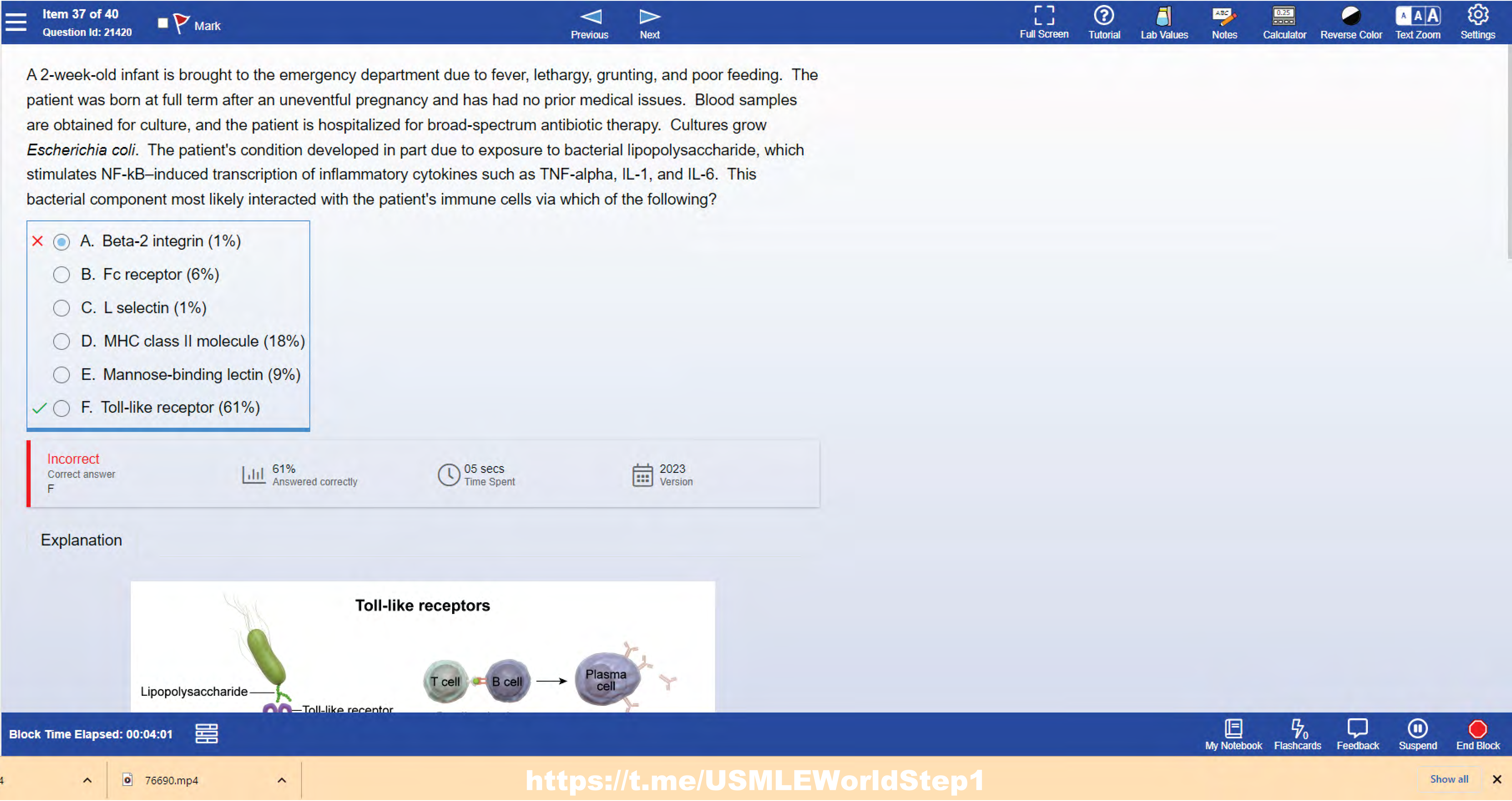
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- ✗ ● A. Beta-2 integrin (1%)
- ○ B. Fc receptor (6%)
- ○ C. L selectin (1%)
- ○ D. MHC class II molecule (18%)
- ○ E. Mannose-binding lectin (9%)
- ✓ ○ F. Toll-like receptor (61%)

Incorrect
Correct answer
F

61%
Answered correctly

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Explanation

Toll-like receptors

Lipopolysaccharide
Toll-like receptor
T cell
B cell
Plasma cell
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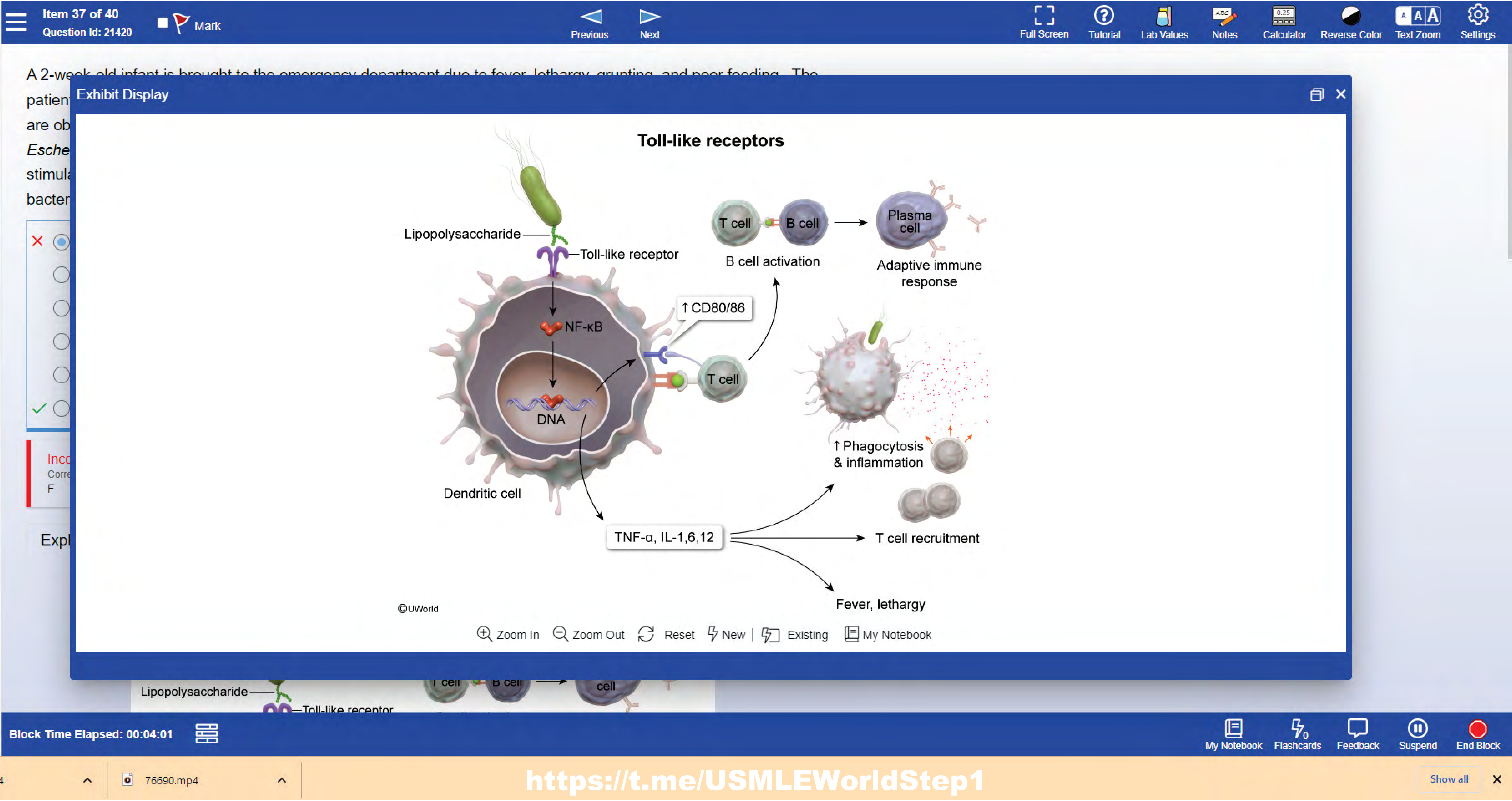
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Toll-like receptors
Lipopolysaccharide
Toll-like receptor
NF-κB
DNA
Dendritic cell
↑ CD80/86
T cell
T cell
B cell
B cell activation
Plasma cell
Adaptive immune response
↑ Phagocytosis & inflammation
TNF-α, IL-1,6,12
T cell recruitment
Fever, lethargy
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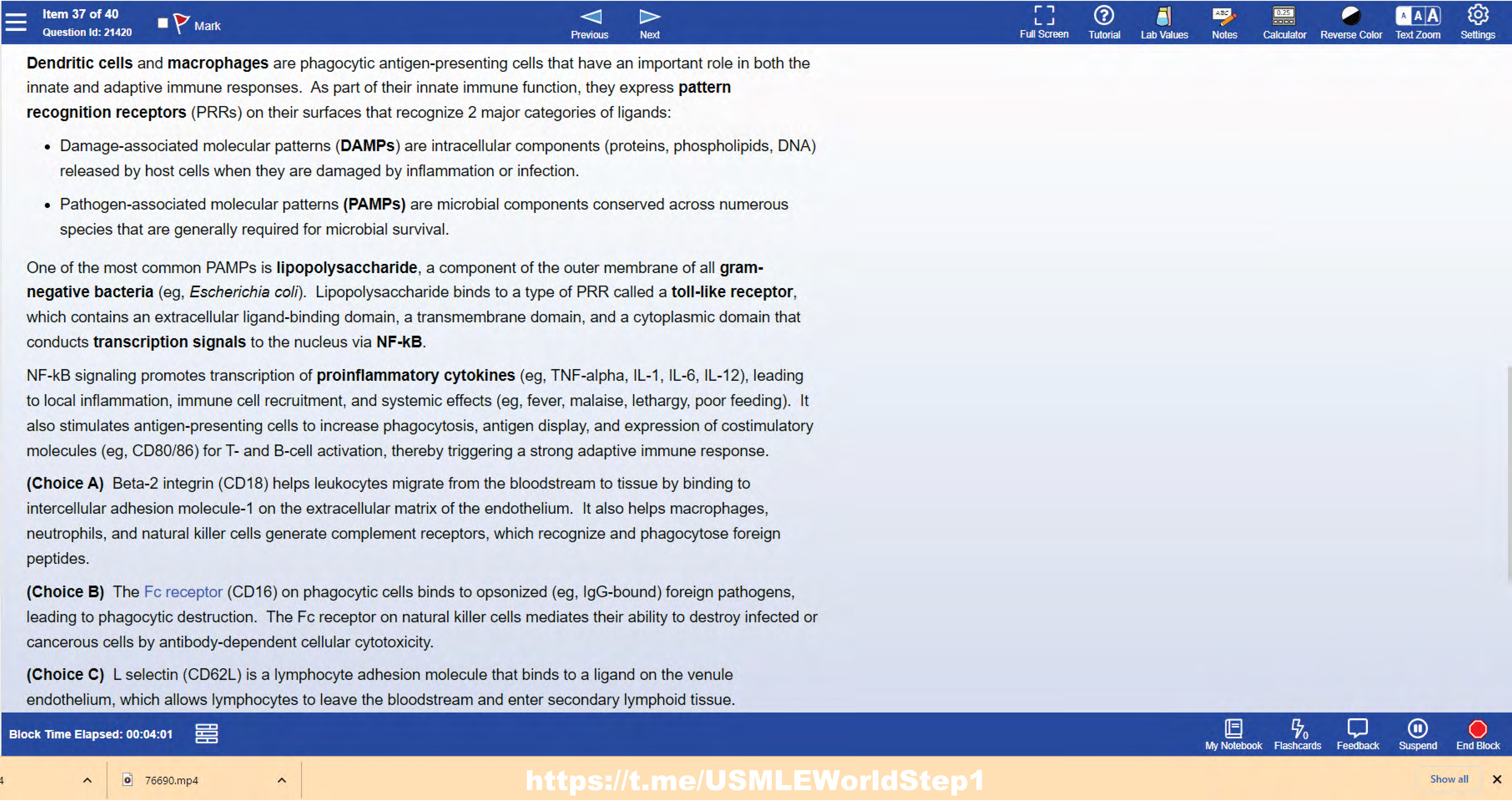

Dendritic cells and **macrophages** are phagocytic antigen-presenting cells that have an important role in both the innate and adaptive immune responses. As part of their innate immune function, they express **pattern recognition receptors** (PRRs) on their surfaces that recognize 2 major categories of ligands:

- Damage-associated molecular patterns (**DAMPs**) are intracellular components (proteins, phospholipids, DNA) released by host cells when they are damaged by inflammation or infection.
- Pathogen-associated molecular patterns **(PAMPs)** are microbial components conserved across numerous species that are generally required for microbial survival.

One of the most common PAMPs is **lipopolysaccharide**, a component of the outer membrane of all **gram-negative bacteria** (eg, *Escherichia coli*). Lipopolysaccharide binds to a type of PRR called a **toll-like receptor**, which contains an extracellular ligand-binding domain, a transmembrane domain, and a cytoplasmic domain that conducts **transcription signals** to the nucleus via **NF-kB**.

NF-kB signaling promotes transcription of **proinflammatory cytokines** (eg, TNF-alpha, IL-1, IL-6, IL-12), leading to local inflammation, immune cell recruitment, and systemic effects (eg, fever, malaise, lethargy, poor feeding). It also stimulates antigen-presenting cells to increase phagocytosis, antigen display, and expression of costimulatory molecules (eg, CD80/86) for T- and B-cell activation, thereby triggering a strong adaptive immune response.

(Choice A) Beta-2 integrin (CD18) helps leukocytes migrate from the bloodstream to tissue by binding to intercellular adhesion molecule-1 on the extracellular matrix of the endothelium. It also helps macrophages, neutrophils, and natural killer cells generate complement receptors, which recognize and phagocytose foreign peptides.

(Choice B) The Fc receptor (CD16) on phagocytic cells binds to opsonized (eg, IgG-bound) foreign pathogens, leading to phagocytic destruction. The Fc receptor on natural killer cells mediates their ability to destroy infected or cancerous cells by antibody-dependent cellular cytotoxicity.

(Choice C) L selectin (CD62L) is a lymphocyte adhesion molecule that binds to a ligand on the venule endothelium, which allows lymphocytes to leave the bloodstream and enter secondary lymphoid tissue.

NF-kB signaling promotes transcription of **proinflammatory cytokines** (eg, TNF-alpha, IL-6, IL-12), leading to local inflammation, immune cell recruitment, and systemic effects (eg, fever, malaise, lethargy, poor feeding). It also stimulates antigen-presenting cells to increase phagocytosis, antigen display, and expression of costimulatory molecules (eg, CD80/86) for T- and B-cell activation, thereby triggering a strong adaptive immune response.

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(Choice C) L selectin (CD62L) is a lymphocyte adhesion molecule that binds to a ligand on the venule endothelium, which allows lymphocytes to leave the bloodstream and enter secondary lymphoid tissue.

(Choice D) Major histocompatibility complex class II molecules are on antigen-presenting cells; they present antigens to the T cell receptor on CD4 cells.

(Choice E) Mannose-binding lectin is a PRR that recognizes microbial carbohydrates and activates the lectin complement pathway.

Educational objective:

Pattern recognition receptors (PRRs) are part of the innate immune response; they recognize damaged host proteins or conserved microbial molecules and trigger inflammation. Toll-like receptors, a type of PRR on macrophages and dendritic cells, recognize lipopolysaccharide and promote the release of inflammatory cytokines (eg, IL-1/6/12, TNF-alpha) via NF-kB signaling.

References

- Pattern recognition receptors and inflammation.

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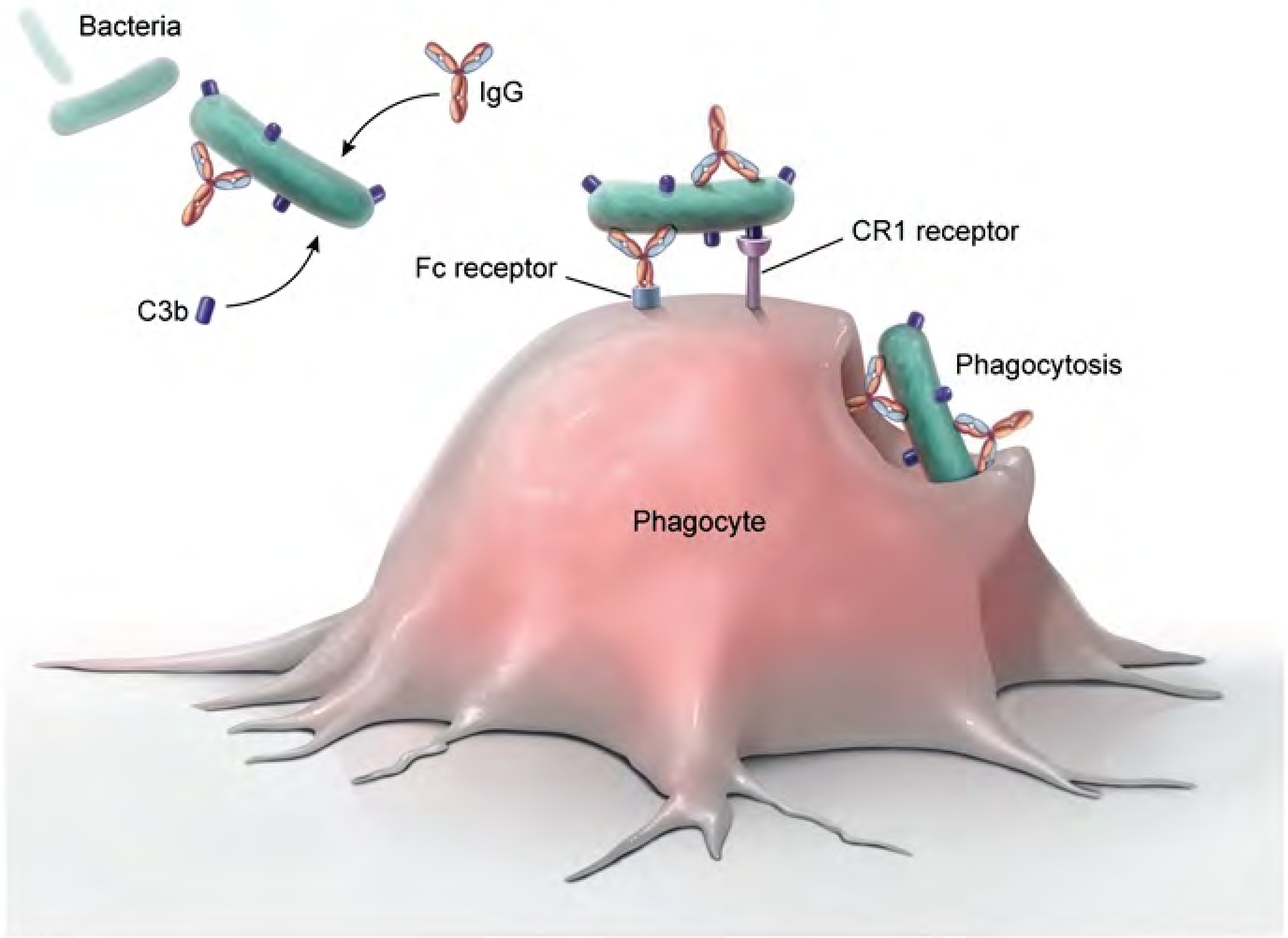
Opsonization & phagocytosis


Bacteria
IgG
C3b
Fc receptor
CR1 receptor
Phagocytosis
Phagocyte

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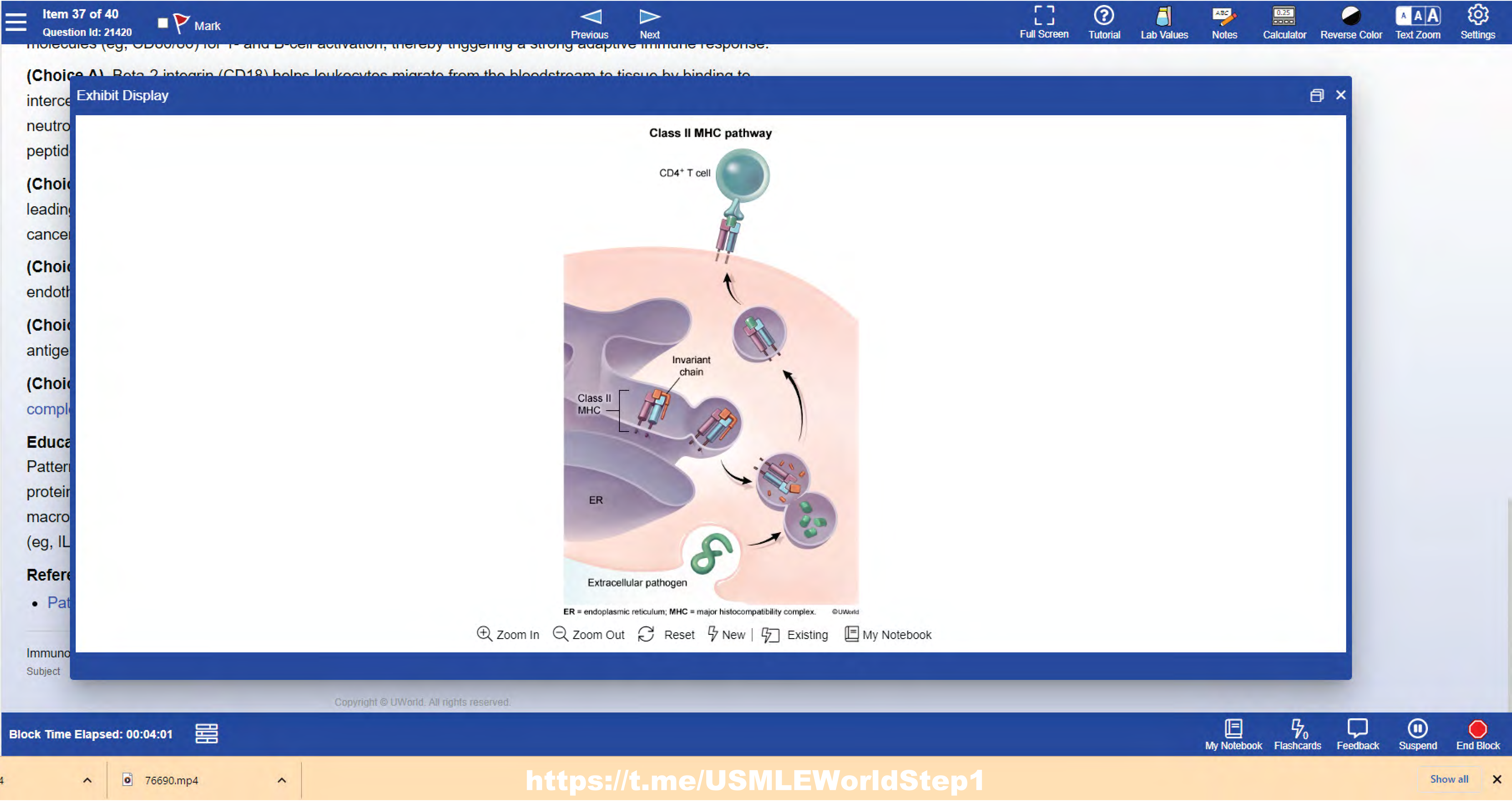
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Class II MHC pathway

CD4+ T cell
Invariant chain
Class II MHC
ER
Extracellular pathogen

ER = endoplasmic reticulum; **MHC** = major histocompatibility complex.

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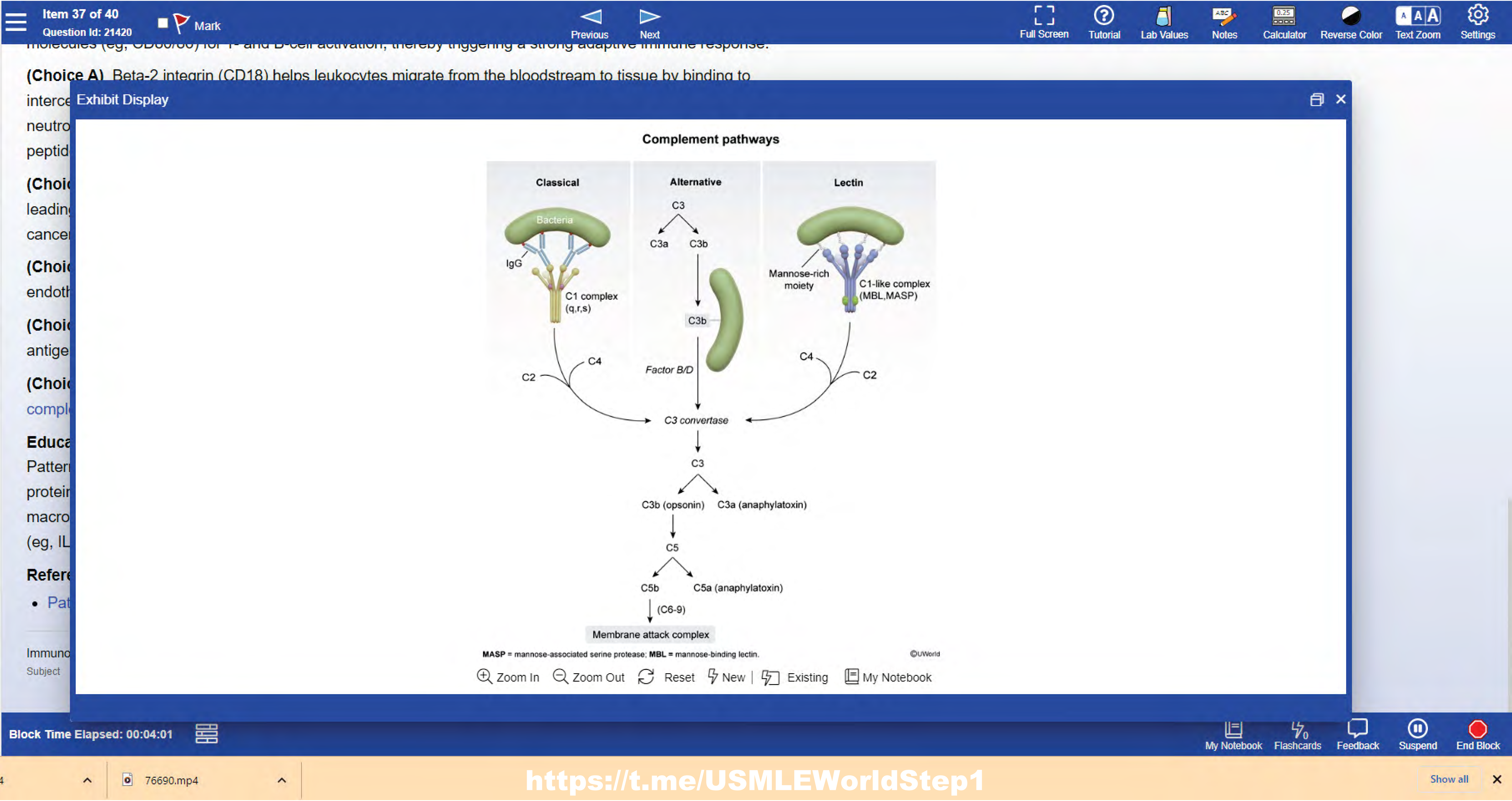

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Complement pathways

Classical
Alternative
Lectin
Bacteria
IgG
C1 complex
(q,r,s)
C3
C3a
C3b
C3b
Factor B/D
Mannose-rich
moiety
C1-like complex
(MBL,MASP)
C4
C2
C2
C4
C3 convertase
C3
C3b (opsonin)
C3a (anaphylatoxin)
C5
C5b
C5a (anaphylatoxin)
(C6-9)
Membrane attack complex

MASP = mannose-associated serine protease; **MBL** = mannose-binding lectin.

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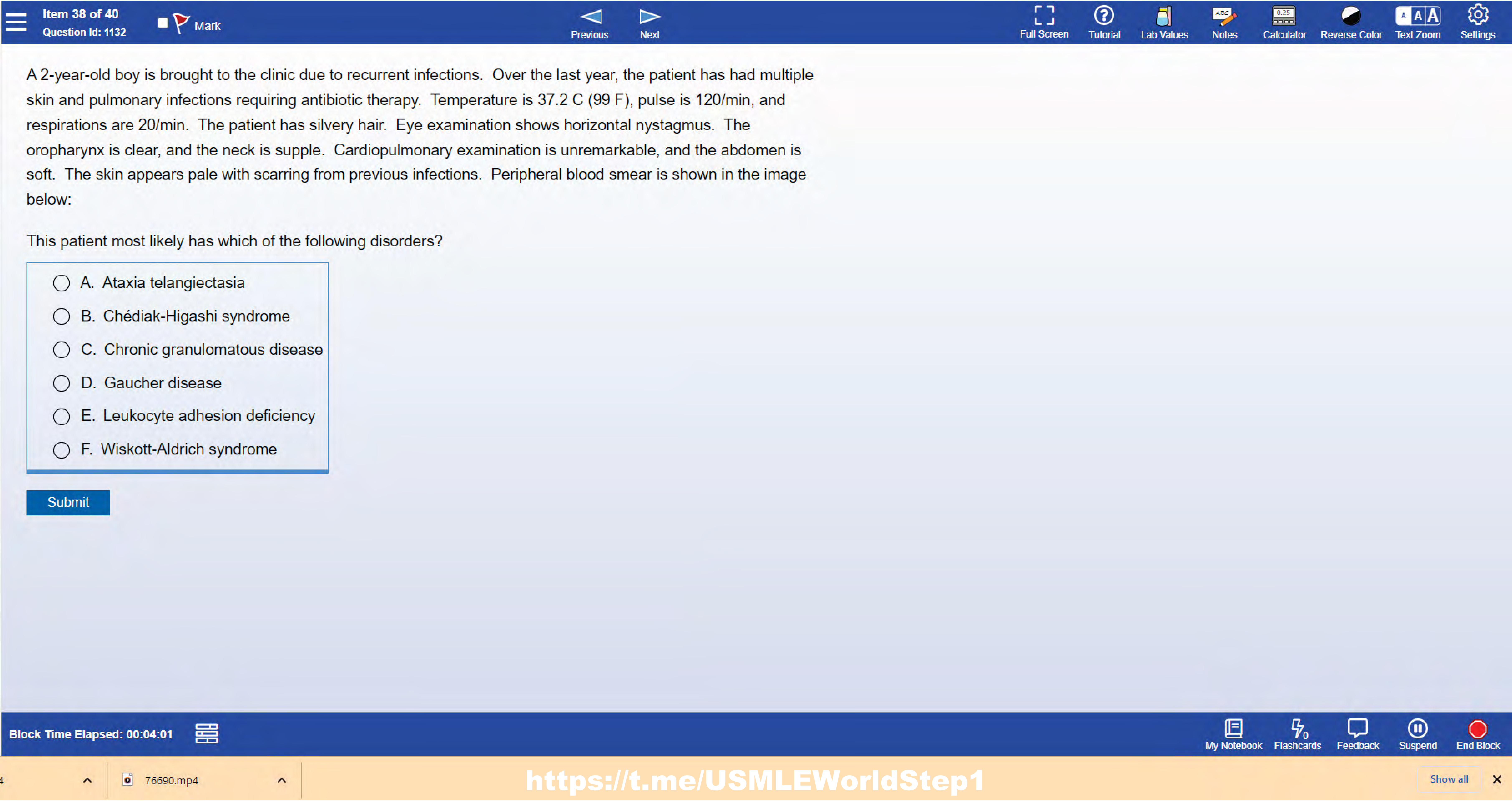
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A 2-year-old boy is brought to the clinic due to recurrent infections. Over the last year, the patient has had multiple skin and pulmonary infections requiring antibiotic therapy. Temperature is 37.2 C (99 F), pulse is 120/min, and respirations are 20/min. The patient has silvery hair. Eye examination shows horizontal nystagmus. The oropharynx is clear, and the neck is supple. Cardiopulmonary examination is unremarkable, and the abdomen is soft. The skin appears pale with scarring from previous infections. Peripheral blood smear is shown in the image below:

This patient most likely has which of the following disorders?

- ○ A. Ataxia telangiectasia
- ○ B. Chédiak-Higashi syndrome
- ○ C. Chronic granulomatous disease
- ○ D. Gaucher disease
- ○ E. Leukocyte adhesion deficiency
- ○ F. Wiskott-Aldrich syndrome

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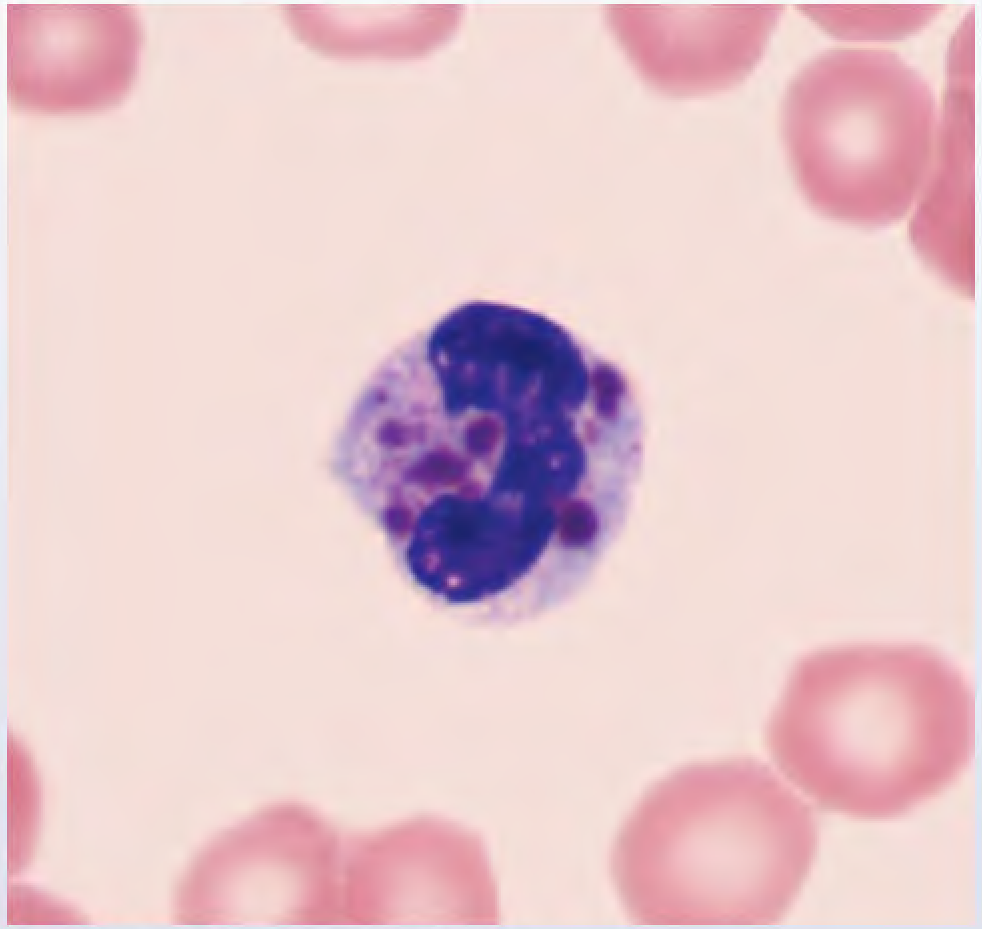
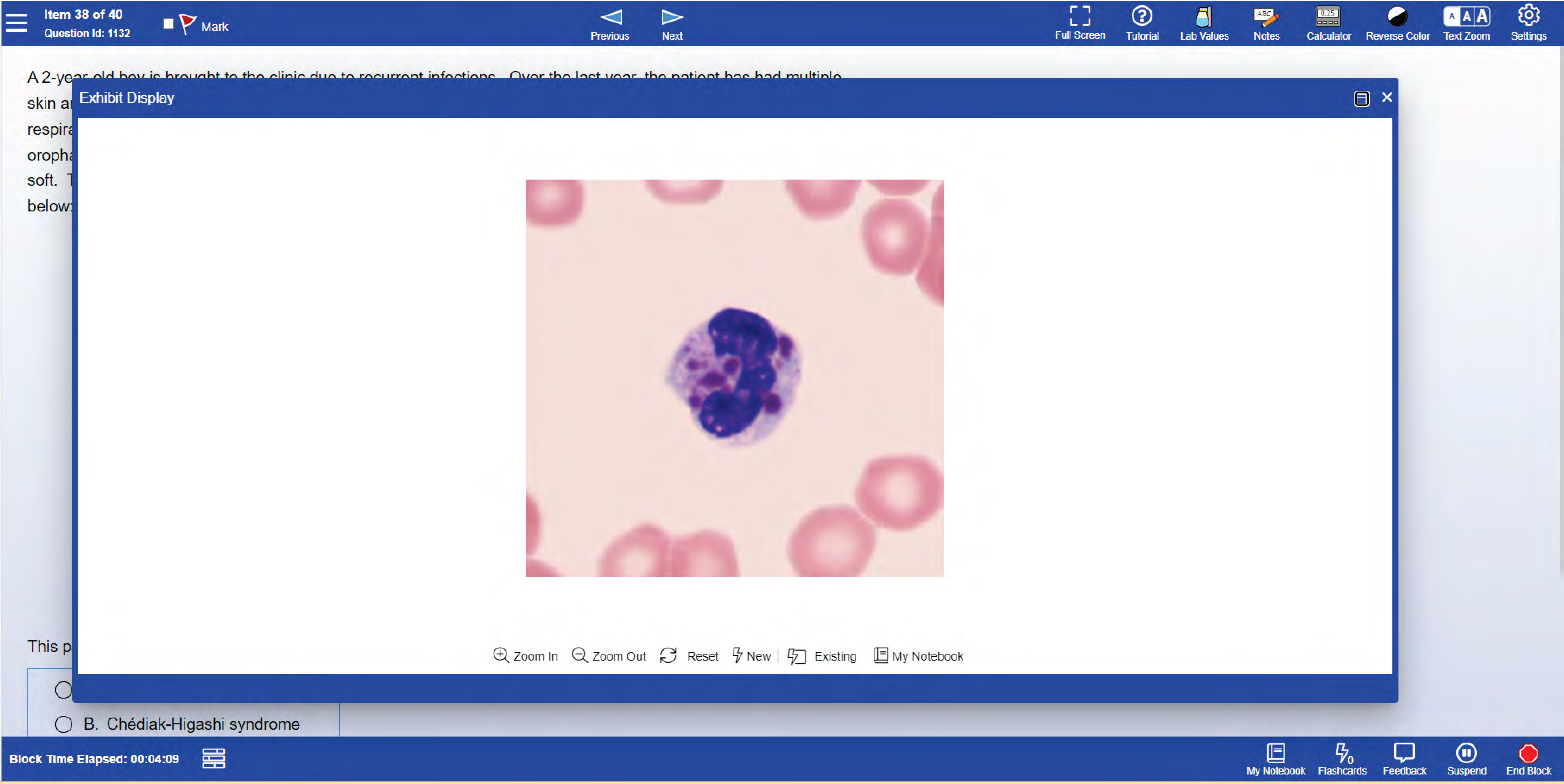


This patient most likely has which of the following disorders?

○ A. Ataxia telangiectasia

○ B. Chédiak-Higashi syndrome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○ B. Chédiak-Higashi syndrome

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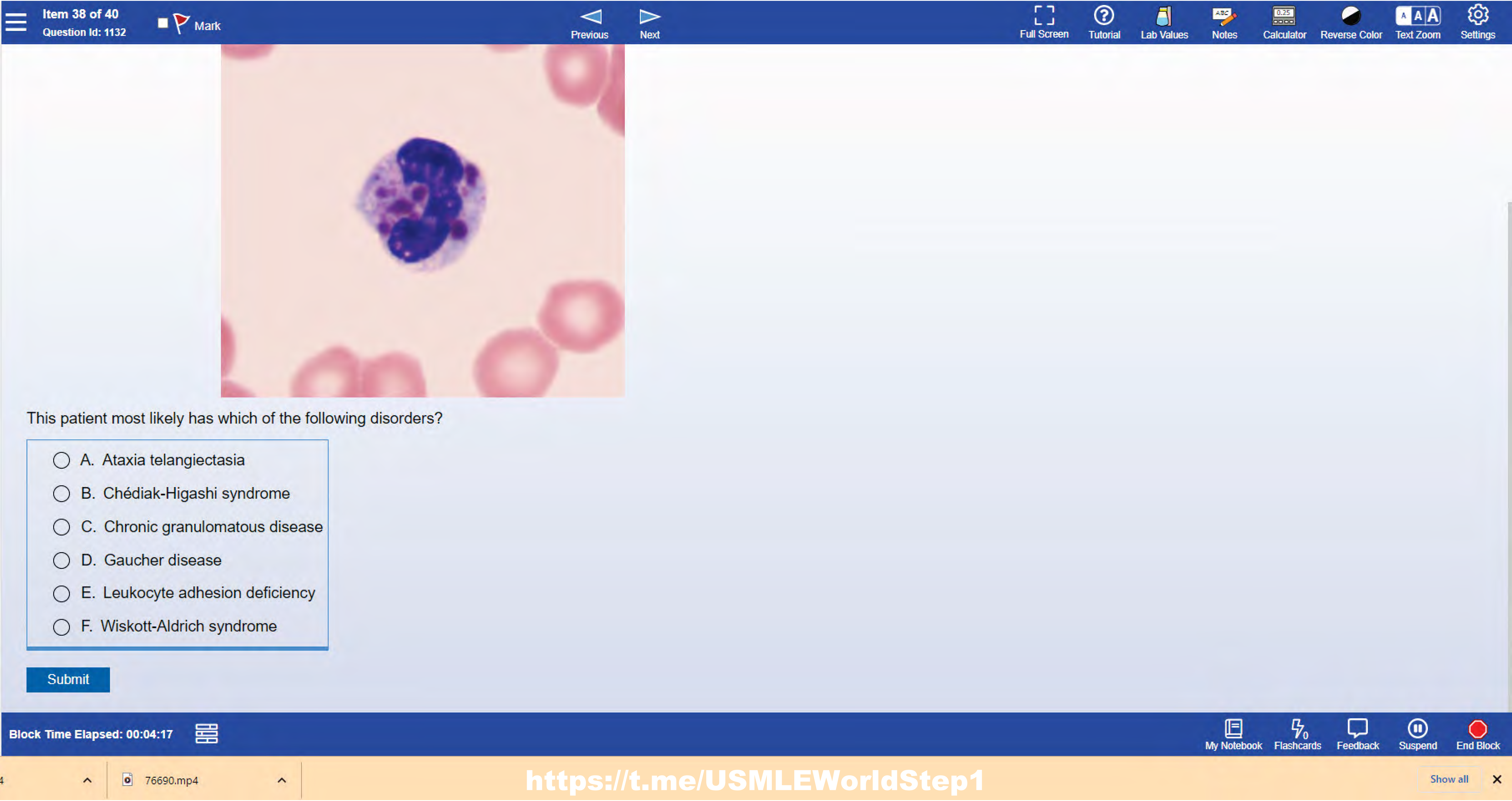
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This patient most likely has which of the following disorders?

- ○ A. Ataxia telangiectasia
- ○ B. Chédiak-Higashi syndrome
- ○ C. Chronic granulomatous disease
- ○ D. Gaucher disease
- ○ E. Leukocyte adhesion deficiency
- ○ F. Wiskott-Aldrich syndrome

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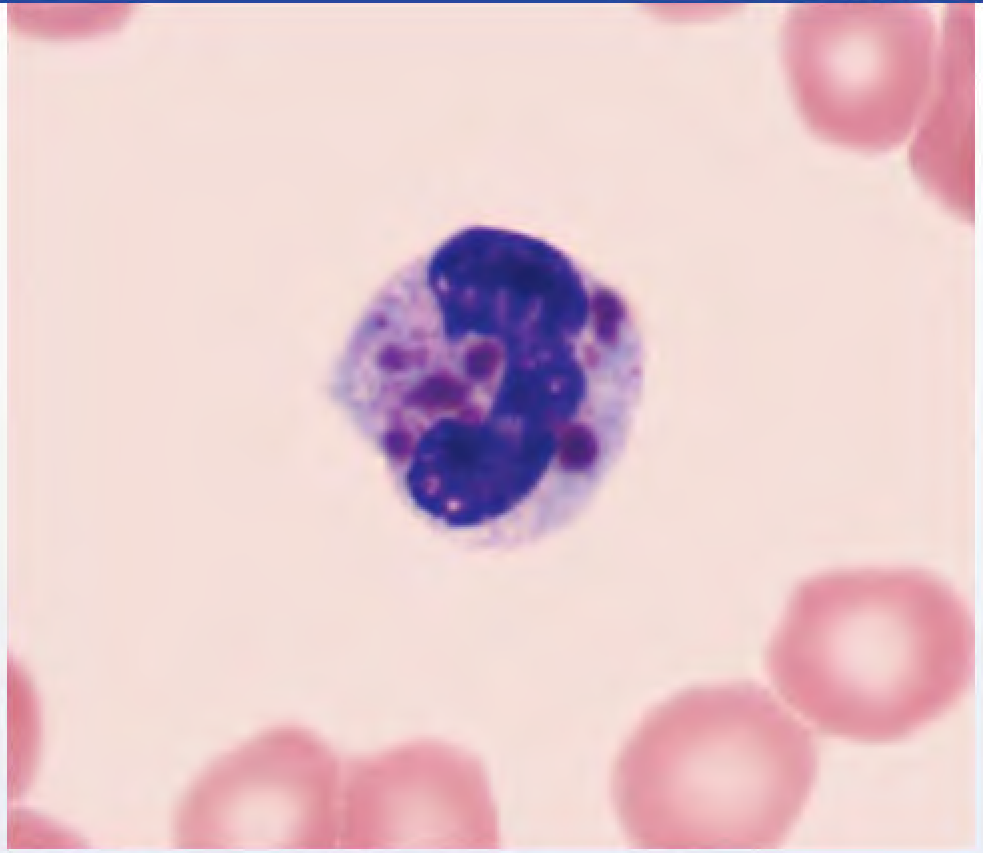

This patient most likely has which of the following disorders?

- ○ A. Ataxia telangiectasia (2%)
- ✓ ● B. Chédiak-Higashi syndrome (70%)
- ○ C. Chronic granulomatous disease (9%)
- ○ D. Gaucher disease (3%)
- ○ E. Leukocyte adhesion deficiency (3%)
- ○ F. Wiskott-Aldrich syndrome (9%)

Correct

70%
Answered correctly

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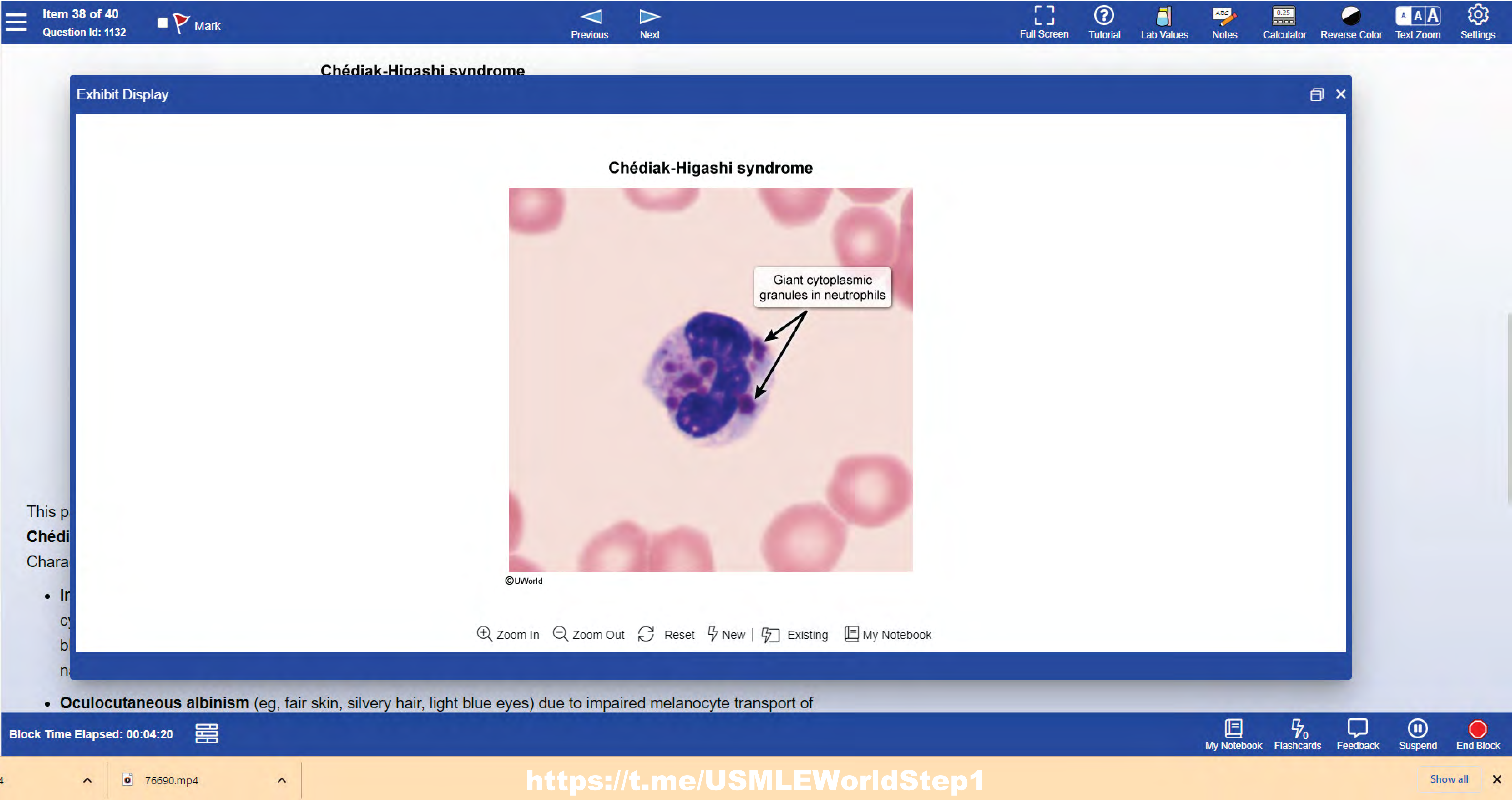
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Chédiak-Higashi syndrome

Chédiak-Higashi syndrome

Giant cytoplasmic granules in neutrophils

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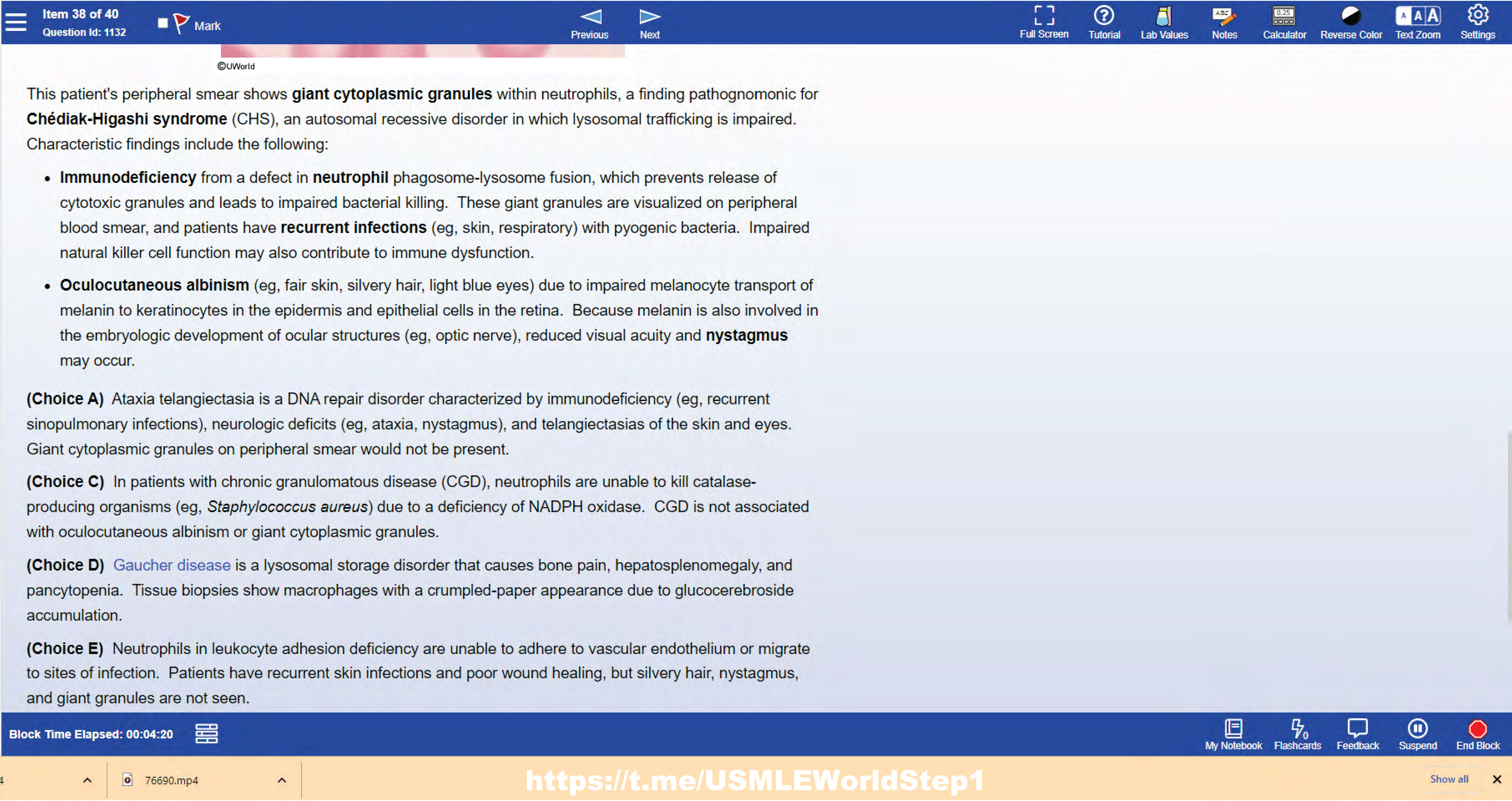
- **Oculocutaneous albinism** (eg, fair skin, silvery hair, light blue eyes) due to impaired melanocyte transport of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This patient's peripheral smear shows **giant cytoplasmic granules** within neutrophils, a finding pathognomonic for **Chédiak-Higashi syndrome** (CHS), an autosomal recessive disorder in which lysosomal trafficking is impaired. Characteristic findings include the following:

- **Immunodeficiency** from a defect in **neutrophil** phagosome-lysosome fusion, which prevents release of cytotoxic granules and leads to impaired bacterial killing. These giant granules are visualized on peripheral blood smear, and patients have **recurrent infections** (eg, skin, respiratory) with pyogenic bacteria. Impaired natural killer cell function may also contribute to immune dysfunction.
- **Oculocutaneous albinism** (eg, fair skin, silvery hair, light blue eyes) due to impaired melanocyte transport of melanin to keratinocytes in the epidermis and epithelial cells in the retina. Because melanin is also involved in the embryologic development of ocular structures (eg, optic nerve), reduced visual acuity and **nystagmus** may occur.

(Choice A) Ataxia telangiectasia is a DNA repair disorder characterized by immunodeficiency (eg, recurrent sinopulmonary infections), neurologic deficits (eg, ataxia, nystagmus), and telangiectasias of the skin and eyes. Giant cytoplasmic granules on peripheral smear would not be present.

(Choice C) In patients with chronic granulomatous disease (CGD), neutrophils are unable to kill catalase-producing organisms (eg, *Staphylococcus aureus*) due to a deficiency of NADPH oxidase. CGD is not associated with oculocutaneous albinism or giant cytoplasmic granules.

(Choice D) Gaucher disease is a lysosomal storage disorder that causes bone pain, hepatosplenomegaly, and pancytopenia. Tissue biopsies show macrophages with a crumpled-paper appearance due to glucocerebroside accumulation.

(Choice E) Neutrophils in leukocyte adhesion deficiency are unable to adhere to vascular endothelium or migrate to sites of infection. Patients have recurrent skin infections and poor wound healing, but silvery hair, nystagmus, and giant granules are not seen.

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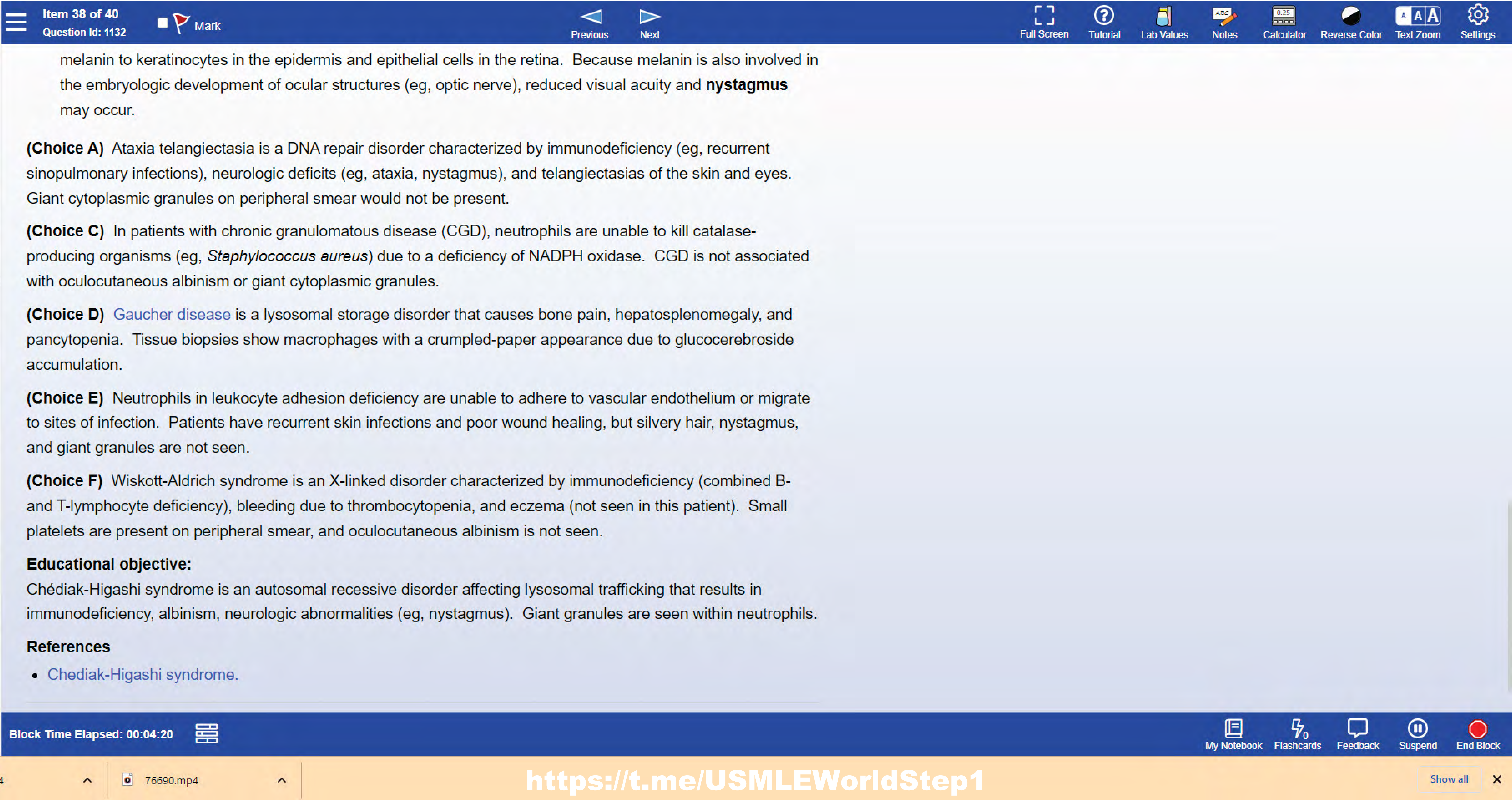
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(Choice E) Neutrophils in leukocyte adhesion deficiency are unable to adhere to vascular endothelium or migrate to sites of infection. Patients have recurrent skin infections and poor wound healing, but silvery hair, nystagmus, and giant granules are not seen.

(Choice F) Wiskott-Aldrich syndrome is an X-linked disorder characterized by immunodeficiency (combined B- and T-lymphocyte deficiency), bleeding due to thrombocytopenia, and eczema (not seen in this patient). Small platelets are present on peripheral smear, and oculocutaneous albinism is not seen.

Educational objective:
Chédiak-Higashi syndrome is an autosomal recessive disorder affecting lysosomal trafficking that results in immunodeficiency, albinism, neurologic abnormalities (eg, nystagmus). Giant granules are seen within neutrophils.

References

- Chediak-Higashi syndrome.

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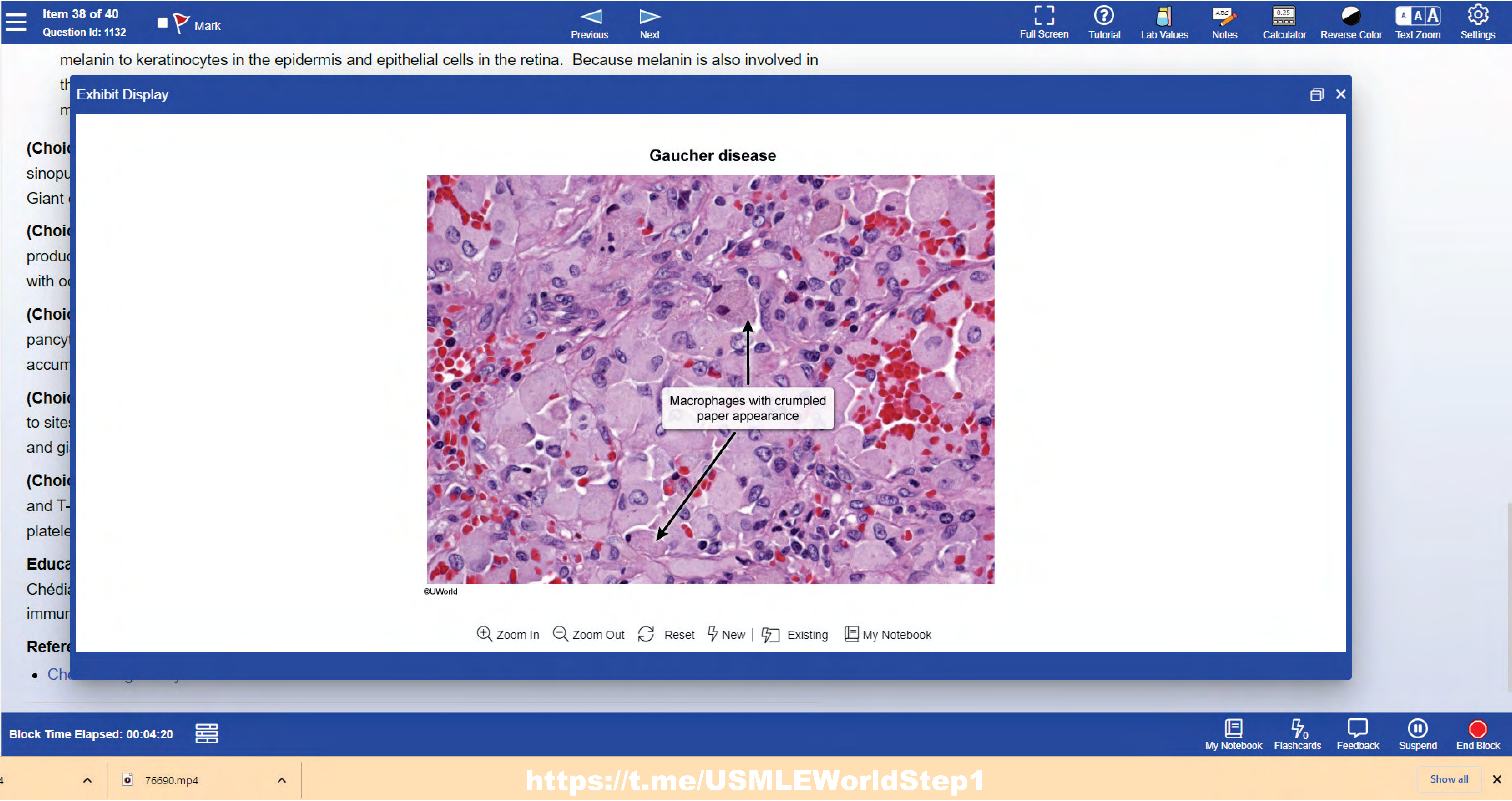
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Gaucher disease

Macrophages with crumpled paper appearance

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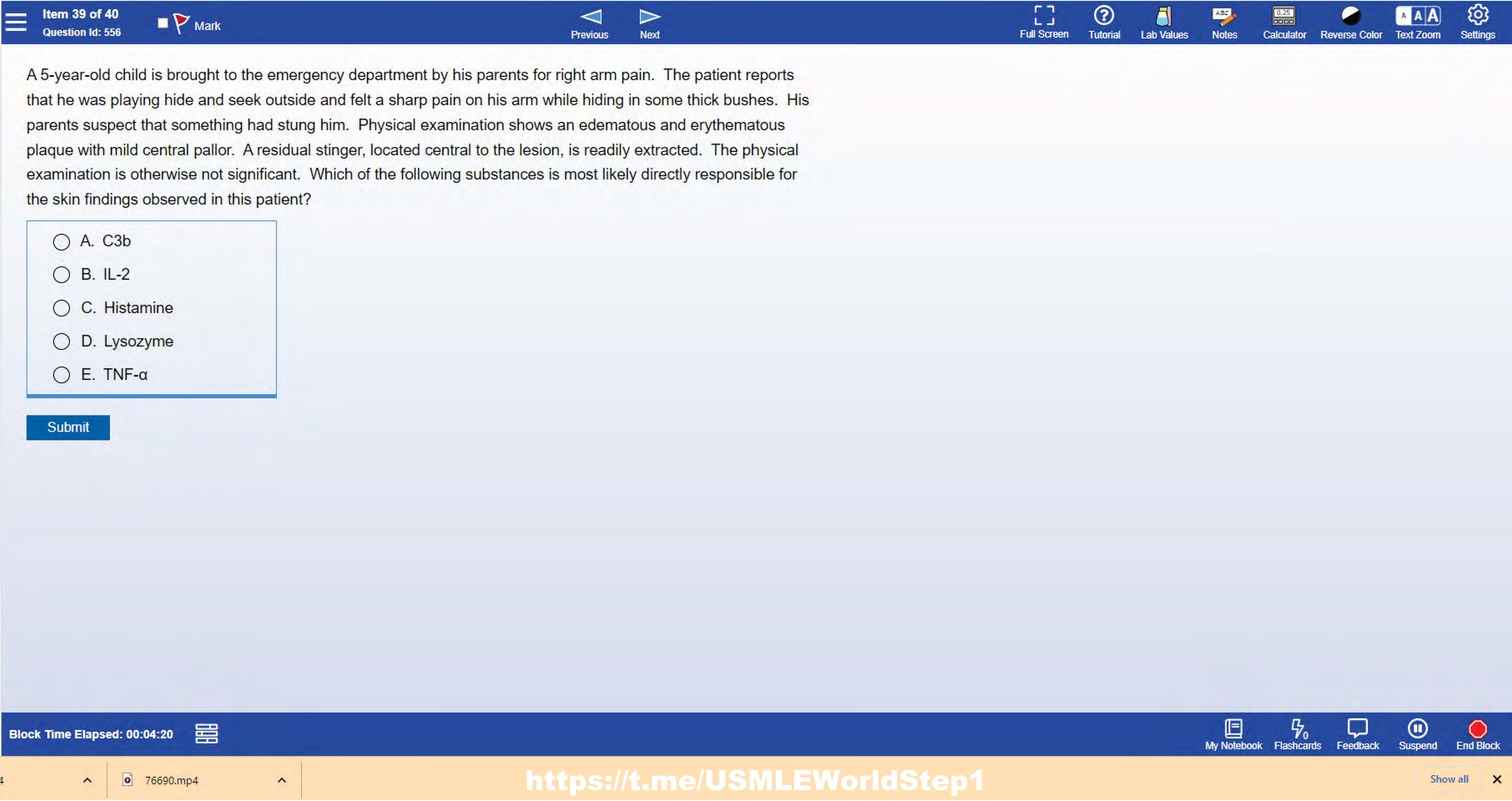
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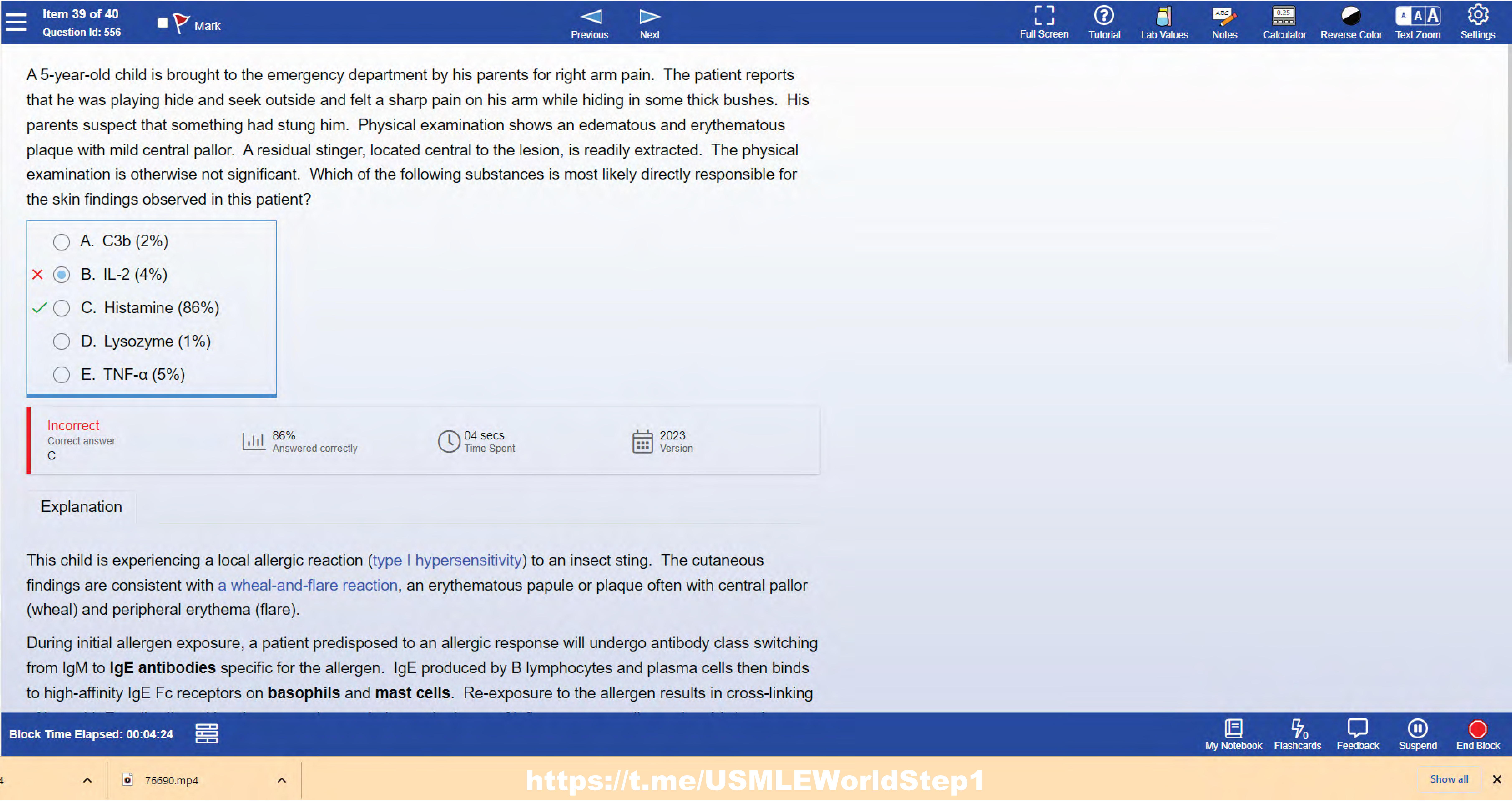
A 5-year-old child is brought to the emergency department by his parents for right arm pain. The patient reports that he was playing hide and seek outside and felt a sharp pain on his arm while hiding in some thick bushes. His parents suspect that something had stung him. Physical examination shows an edematous and erythematous plaque with mild central pallor. A residual stinger, located central to the lesion, is readily extracted. The physical examination is otherwise not significant. Which of the following substances is most likely directly responsible for the skin findings observed in this patient?

○ A. C3b
○ B. IL-2
○ C. Histamine
○ D. Lysozyme
○ E. TNF-α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○ A. C3b (2%)

✗ ● B. IL-2 (4%)

✓ ○ C. Histamine (86%)

○ D. Lysozyme (1%)

○ E. TNF-α (5%)

Incorrect
Correct answer
C

86%
Answered correctly

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Explanation

This child is experiencing a local allergic reaction (type I hypersensitivity) to an insect sting. The cutaneous findings are consistent with a wheal-and-flare reaction, an erythematous papule or plaque often with central pallor (wheal) and peripheral erythema (flare).

During initial allergen exposure, a patient predisposed to an allergic response will undergo antibody class switching from IgM to **IgE antibodies** specific for the allergen. IgE produced by B lymphocytes and plasma cells then binds to high-affinity IgE Fc receptors on **basophils** and **mast cells**. Re-exposure to the allergen results in cross-linking

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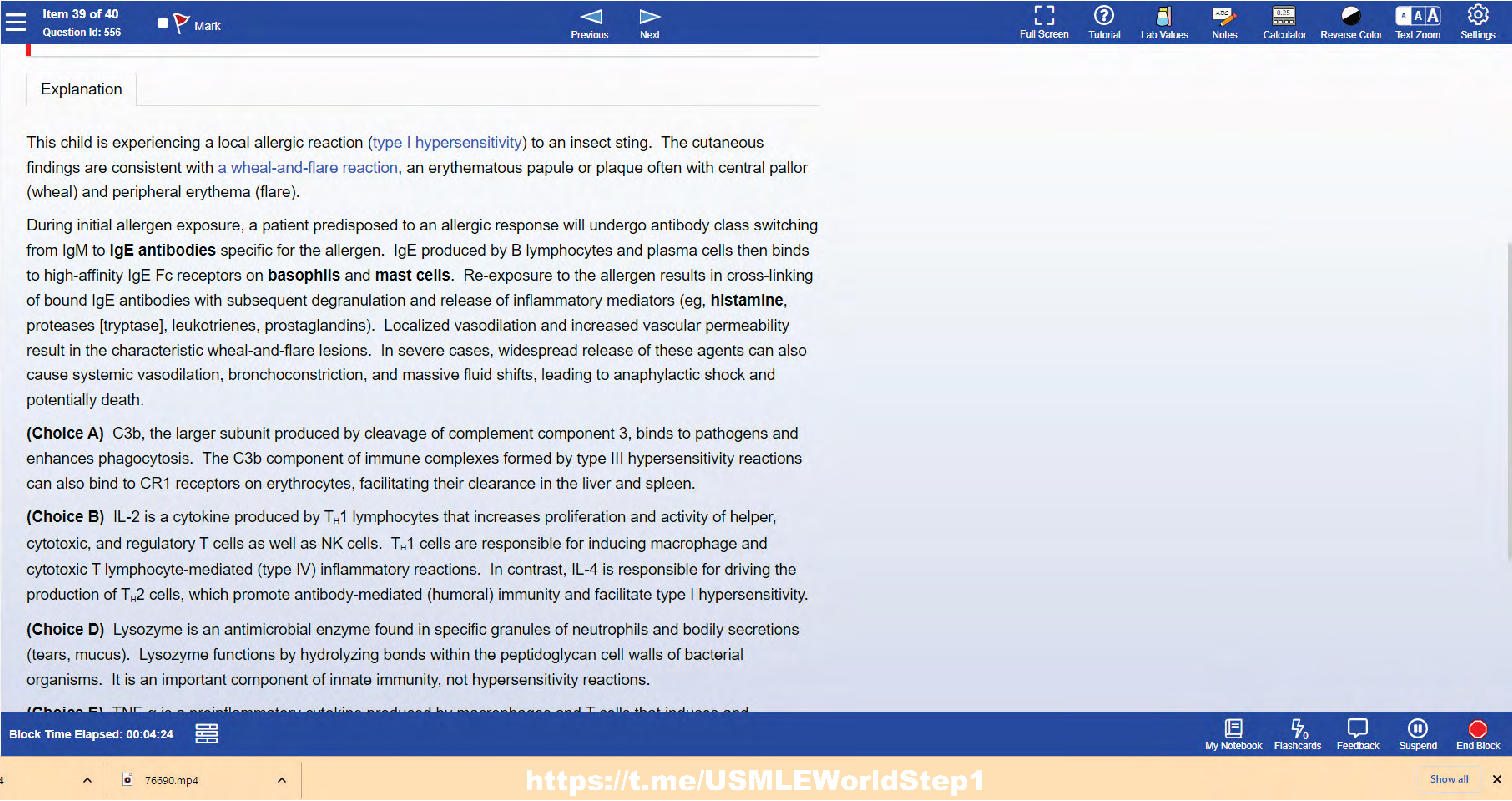


Explanation

This child is experiencing a local allergic reaction (type I hypersensitivity) to an insect sting. The cutaneous findings are consistent with a wheal-and-flare reaction, an erythematous papule or plaque often with central pallor (wheal) and peripheral erythema (flare).

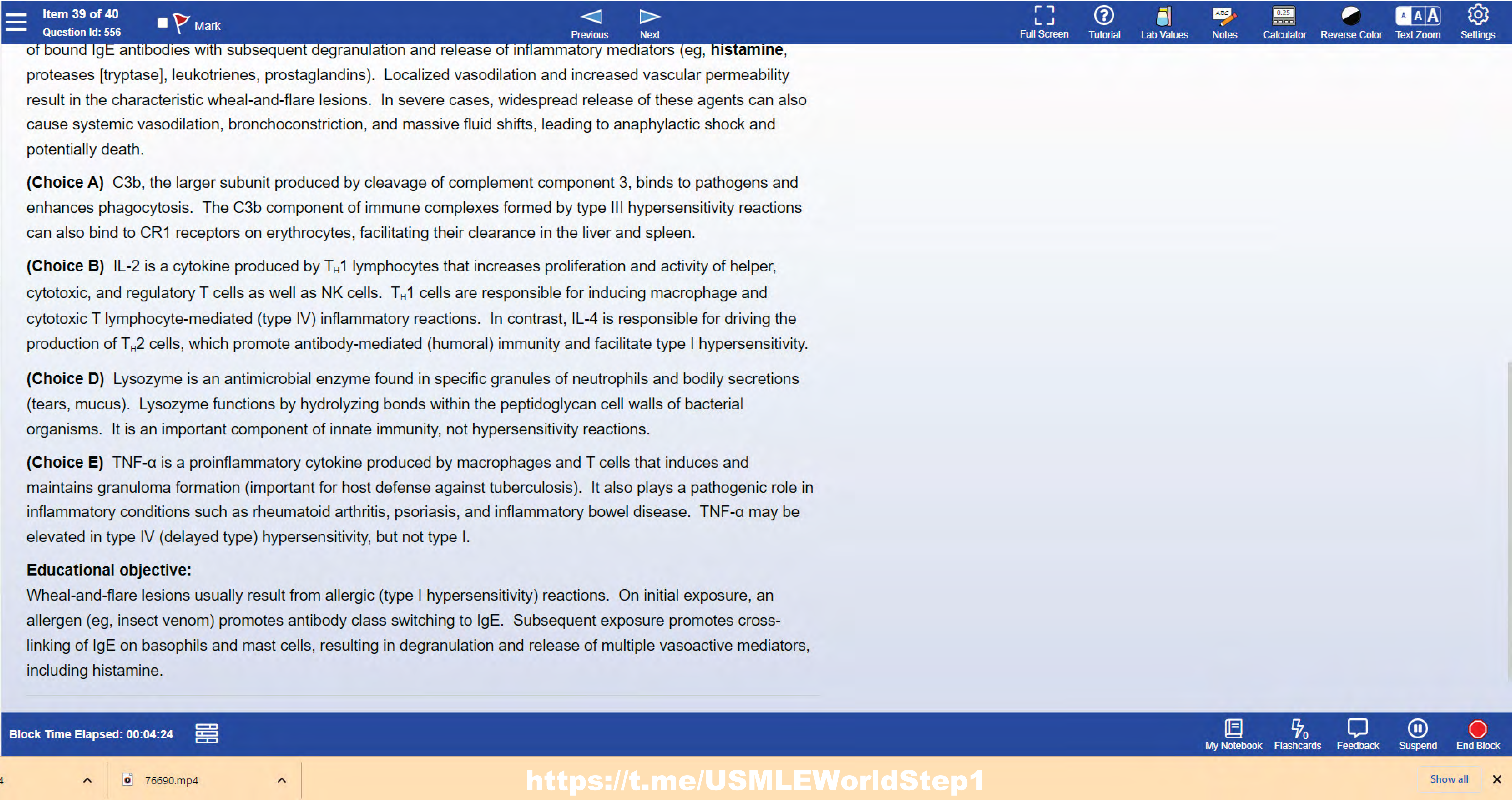
During initial allergen exposure, a patient predisposed to an allergic response will undergo antibody class switching from IgM to **IgE antibodies** specific for the allergen. IgE produced by B lymphocytes and plasma cells then binds to high-affinity IgE Fc receptors on **basophils** and **mast cells**. Re-exposure to the allergen results in cross-linking of bound IgE antibodies with subsequent degranulation and release of inflammatory mediators (eg, **histamine**, proteases [tryptase], leukotrienes, prostaglandins). Localized vasodilation and increased vascular permeability result in the characteristic wheal-and-flare lesions. In severe cases, widespread release of these agents can also cause systemic vasodilation, bronchoconstriction, and massive fluid shifts, leading to anaphylactic shock and potentially death.

(Choice A) C3b, the larger subunit produced by cleavage of complement component 3, binds to pathogens and enhances phagocytosis. The C3b component of immune complexes formed by type III hypersensitivity reactions can also bind to CR1 receptors on erythrocytes, facilitating their clearance in the liver and spleen.

(Choice B) IL-2 is a cytokine produced by T_H1 lymphocytes that increases proliferation and activity of helper, cytotoxic, and regulatory T cells as well as NK cells. T_H1 cells are responsible for inducing macrophage and cytotoxic T lymphocyte-mediated (type IV) inflammatory reactions. In contrast, IL-4 is responsible for driving the production of T_H2 cells, which promote antibody-mediated (humoral) immunity and facilitate type I hypersensitivity.

(Choice D) Lysozyme is an antimicrobial enzyme found in specific granules of neutrophils and bodily secretions (tears, mucus). Lysozyme functions by hydrolyzing bonds within the peptidoglycan cell walls of bacterial organisms. It is an important component of innate immunity, not hypersensitivity reactions.

(Choice E) TNF-α is a proinflammatory cytokine produced by macrophages and T cells that induces and



of bound IgE antibodies with subsequent degranulation and release of inflammatory mediators (eg, **histamine**, proteases [tryptase], leukotrienes, prostaglandins). Localized vasodilation and increased vascular permeability result in the characteristic wheal-and-flare lesions. In severe cases, widespread release of these agents can also cause systemic vasodilation, bronchoconstriction, and massive fluid shifts, leading to anaphylactic shock and potentially death.

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(Choice E) TNF-α is a proinflammatory cytokine produced by macrophages and T cells that induces and maintains granuloma formation (important for host defense against tuberculosis). It also plays a pathogenic role in inflammatory conditions such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease. TNF-α may be elevated in type IV (delayed type) hypersensitivity, but not type I.

Educational objective:

Wheal-and-flare lesions usually result from allergic (type I hypersensitivity) reactions. On initial exposure, an allergen (eg, insect venom) promotes antibody class switching to IgE. Subsequent exposure promotes cross-linking of IgE on basophils and mast cells, resulting in degranulation and release of multiple vasoactive mediators, including histamine.

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organisms. It is an important component of innate immunity, not hypersensitivity reactions.

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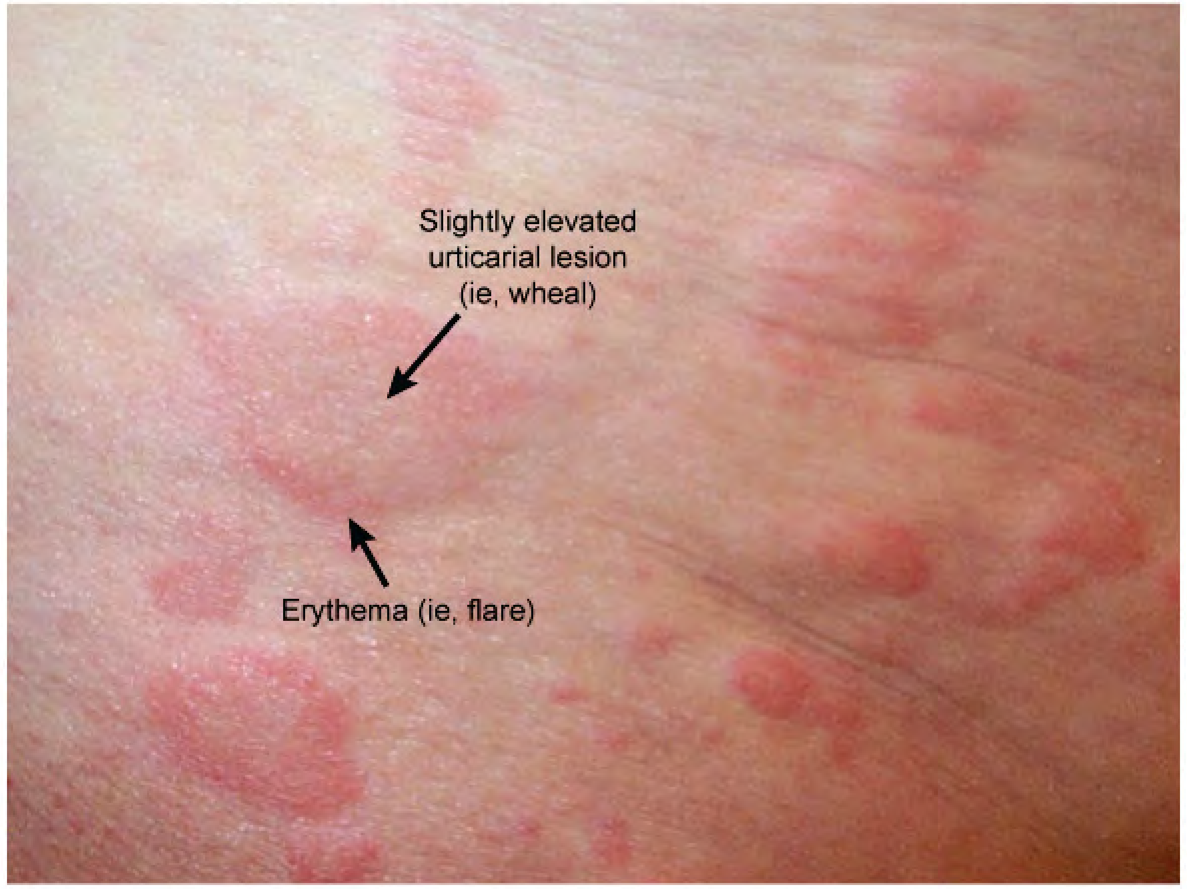
Wheal and flare



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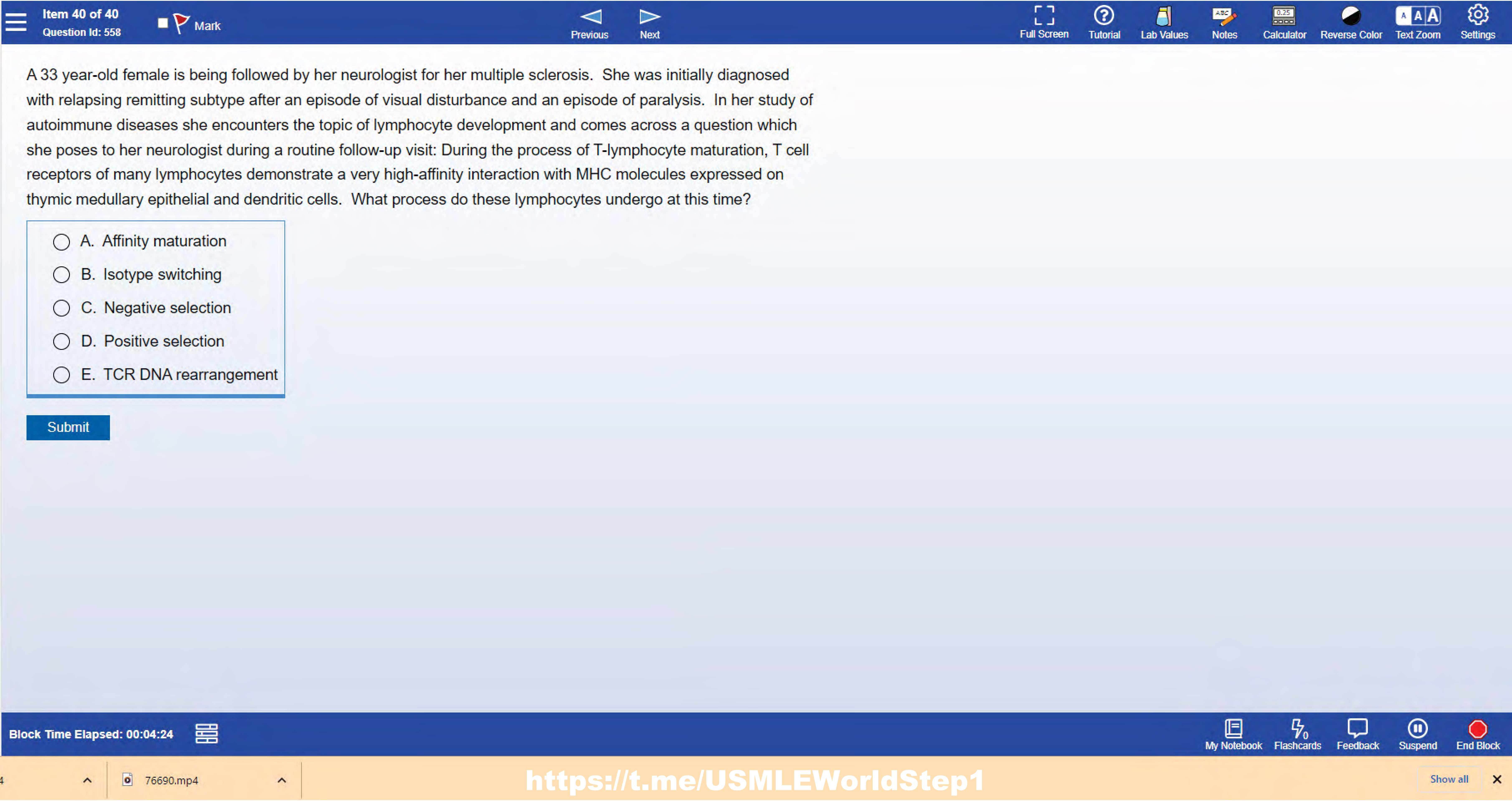
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A 33 year-old female is being followed by her neurologist for her multiple sclerosis. She was initially diagnosed with relapsing remitting subtype after an episode of visual disturbance and an episode of paralysis. In her study of autoimmune diseases she encounters the topic of lymphocyte development and comes across a question which she poses to her neurologist during a routine follow-up visit: During the process of T-lymphocyte maturation, T cell receptors of many lymphocytes demonstrate a very high-affinity interaction with MHC molecules expressed on thymic medullary epithelial and dendritic cells. What process do these lymphocytes undergo at this time?

○ A. Affinity maturation
○ B. Isotype switching
○ C. Negative selection
○ D. Positive selection
○ E. TCR DNA rearrangement

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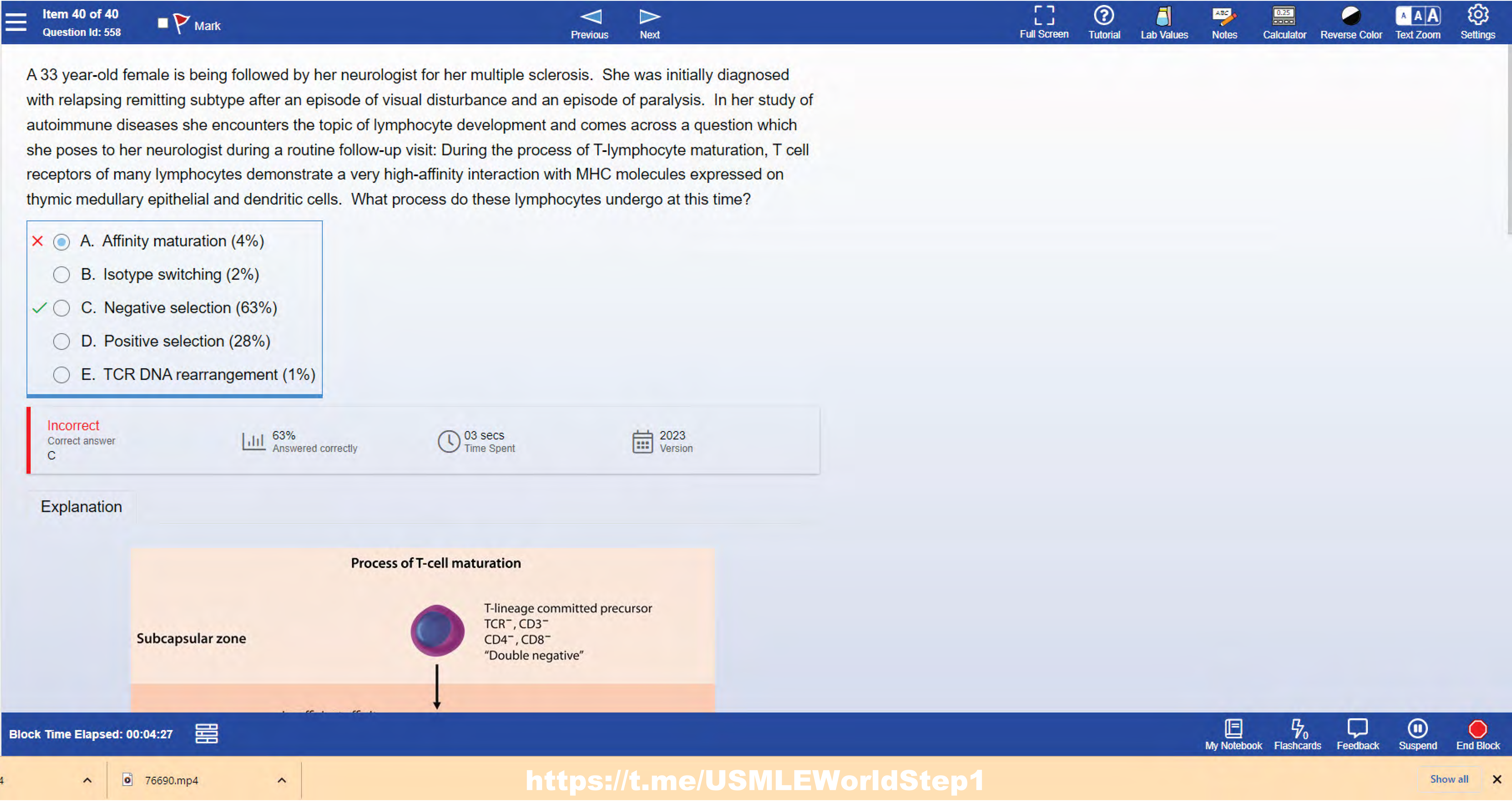
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✗ ● A. Affinity maturation (4%)
○ B. Isotype switching (2%)
✓ ○ C. Negative selection (63%)
○ D. Positive selection (28%)
○ E. TCR DNA rearrangement (1%)

Incorrect
Correct answer
C

63%
Answered correctly

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Explanation

Process of T-cell maturation

Subcapsular zone

T-lineage committed precursor
TCR^-, $CD3^-$
$CD4^-$, $CD8^-$
"Double negative"

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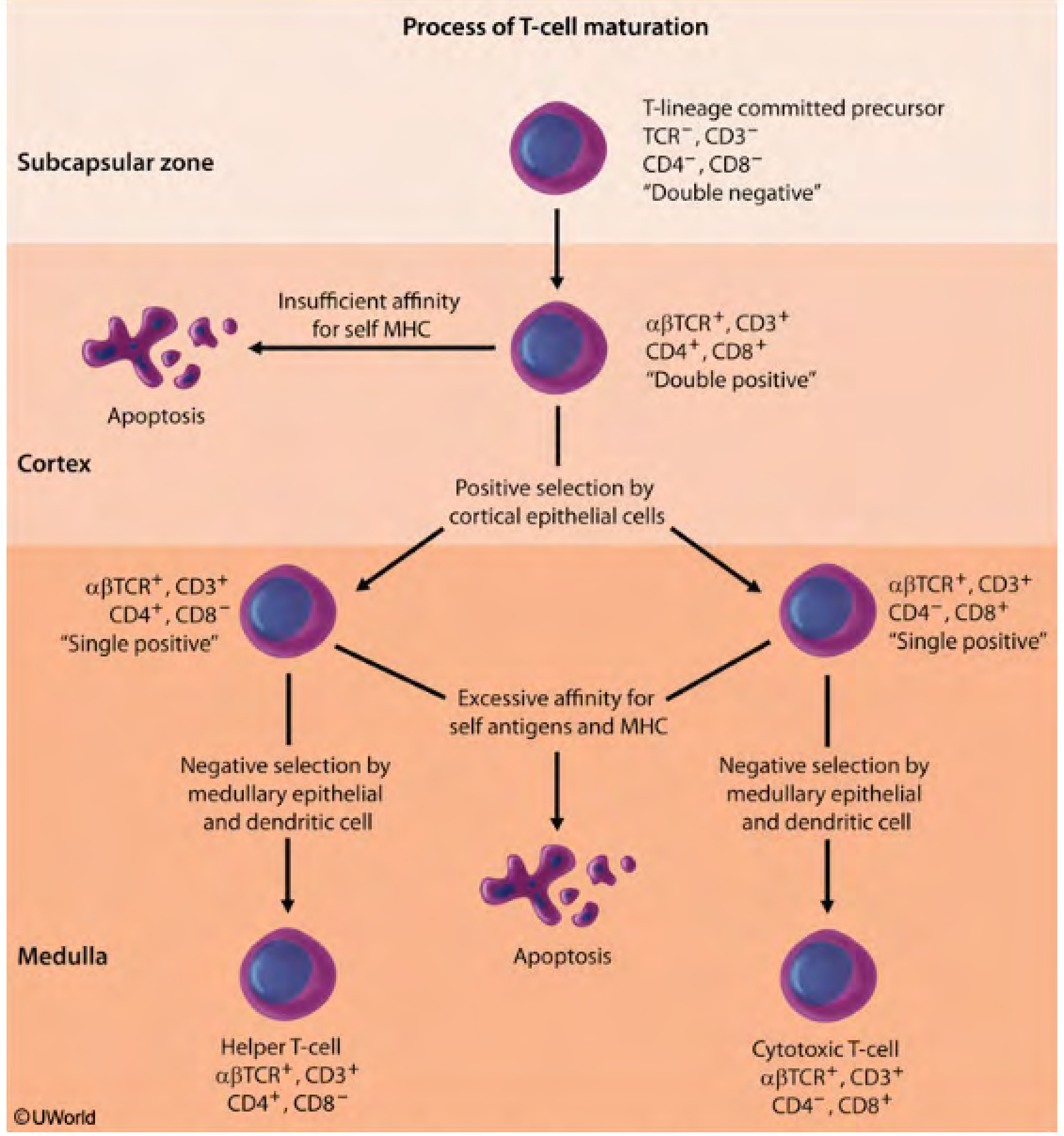
Process of T-cell maturation
Subcapsular zone
T-lineage committed precursor
TCR⁻, CD3⁻
CD4⁻, CD8⁻
"Double negative"
Insufficient affinity for self MHC
Apoptosis
αβTCR⁺, CD3⁺
CD4⁺, CD8⁺
"Double positive"
Cortex
Positive selection by cortical epithelial cells
αβTCR⁺, CD3⁺
CD4⁺, CD8⁻
"Single positive"
αβTCR⁺, CD3⁺
CD4⁻, CD8⁺
"Single positive"
Excessive affinity for self antigens and MHC
Negative selection by medullary epithelial and dendritic cell
Negative selection by medullary epithelial and dendritic cell
Apoptosis
Medulla
Helper T-cell
αβTCR⁺, CD3⁺
CD4⁺, CD8⁻
Cytotoxic T-cell
αβTCR⁺, CD3⁺
CD4⁻, CD8⁺
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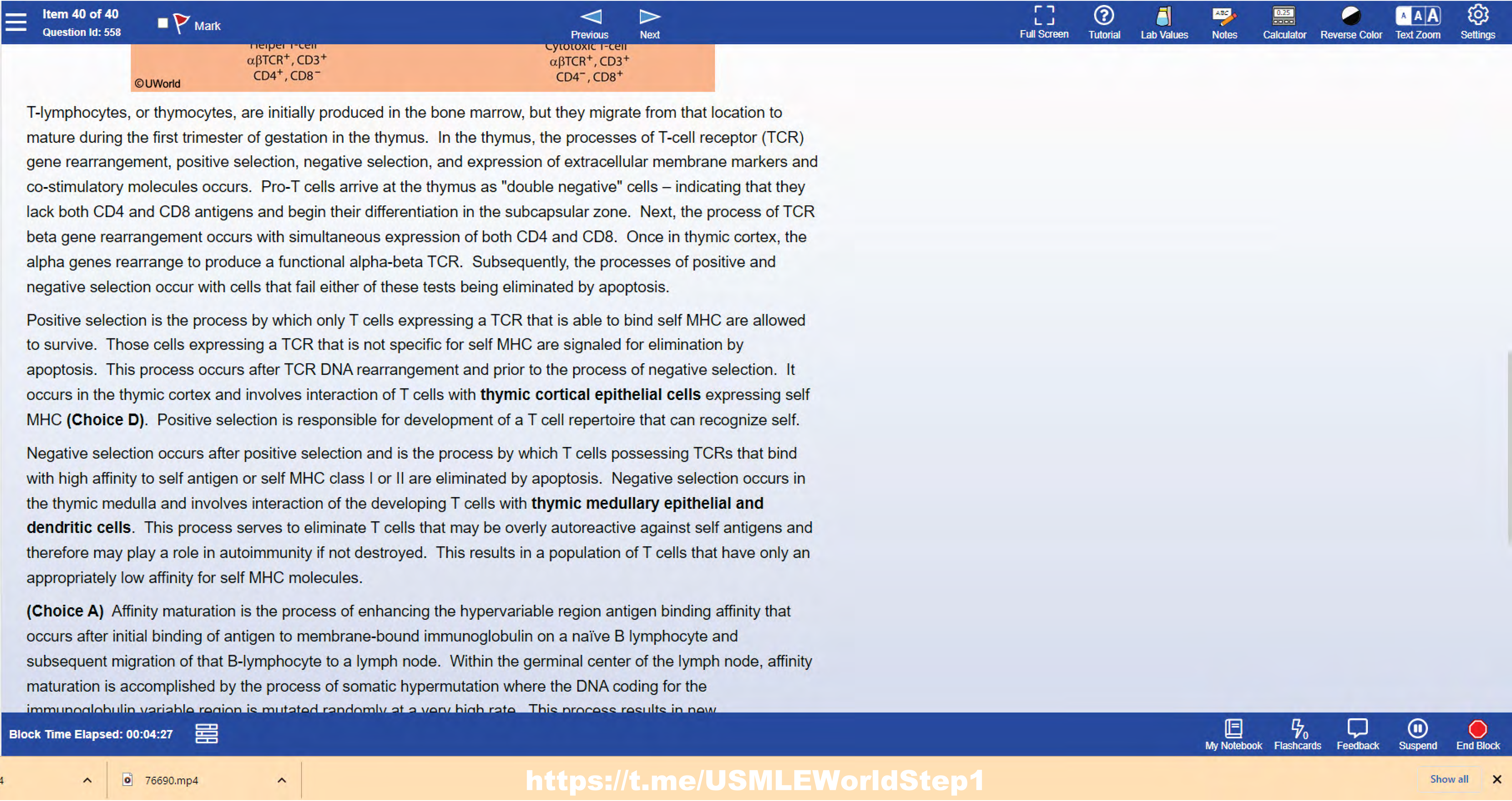
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Helper T-cell
$\alpha\beta TCR^+, CD3^+$
$CD4^+, CD8^-$
Cytotoxic T-cell
$\alpha\beta TCR^+, CD3^+$
$CD4^-, CD8^+$
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T-lymphocytes, or thymocytes, are initially produced in the bone marrow, but they migrate from that location to mature during the first trimester of gestation in the thymus. In the thymus, the processes of T-cell receptor (TCR) gene rearrangement, positive selection, negative selection, and expression of extracellular membrane markers and co-stimulatory molecules occurs. Pro-T cells arrive at the thymus as "double negative" cells – indicating that they lack both CD4 and CD8 antigens and begin their differentiation in the subcapsular zone. Next, the process of TCR beta gene rearrangement occurs with simultaneous expression of both CD4 and CD8. Once in thymic cortex, the alpha genes rearrange to produce a functional alpha-beta TCR. Subsequently, the processes of positive and negative selection occur with cells that fail either of these tests being eliminated by apoptosis.

Positive selection is the process by which only T cells expressing a TCR that is able to bind self MHC are allowed to survive. Those cells expressing a TCR that is not specific for self MHC are signaled for elimination by apoptosis. This process occurs after TCR DNA rearrangement and prior to the process of negative selection. It occurs in the thymic cortex and involves interaction of T cells with **thymic cortical epithelial cells** expressing self MHC **(Choice D)**. Positive selection is responsible for development of a T cell repertoire that can recognize self.

Negative selection occurs after positive selection and is the process by which T cells possessing TCRs that bind with high affinity to self antigen or self MHC class I or II are eliminated by apoptosis. Negative selection occurs in the thymic medulla and involves interaction of the developing T cells with **thymic medullary epithelial and dendritic cells**. This process serves to eliminate T cells that may be overly autoreactive against self antigens and therefore may play a role in autoimmunity if not destroyed. This results in a population of T cells that have only an appropriately low affinity for self MHC molecules.

(Choice A) Affinity maturation is the process of enhancing the hypervariable region antigen binding affinity that occurs after initial binding of antigen to membrane-bound immunoglobulin on a naïve B lymphocyte and subsequent migration of that B-lymphocyte to a lymph node. Within the germinal center of the lymph node, affinity maturation is accomplished by the process of somatic hypermutation where the DNA coding for the immunoglobulin variable region is mutated randomly at a very high rate. This process results in new

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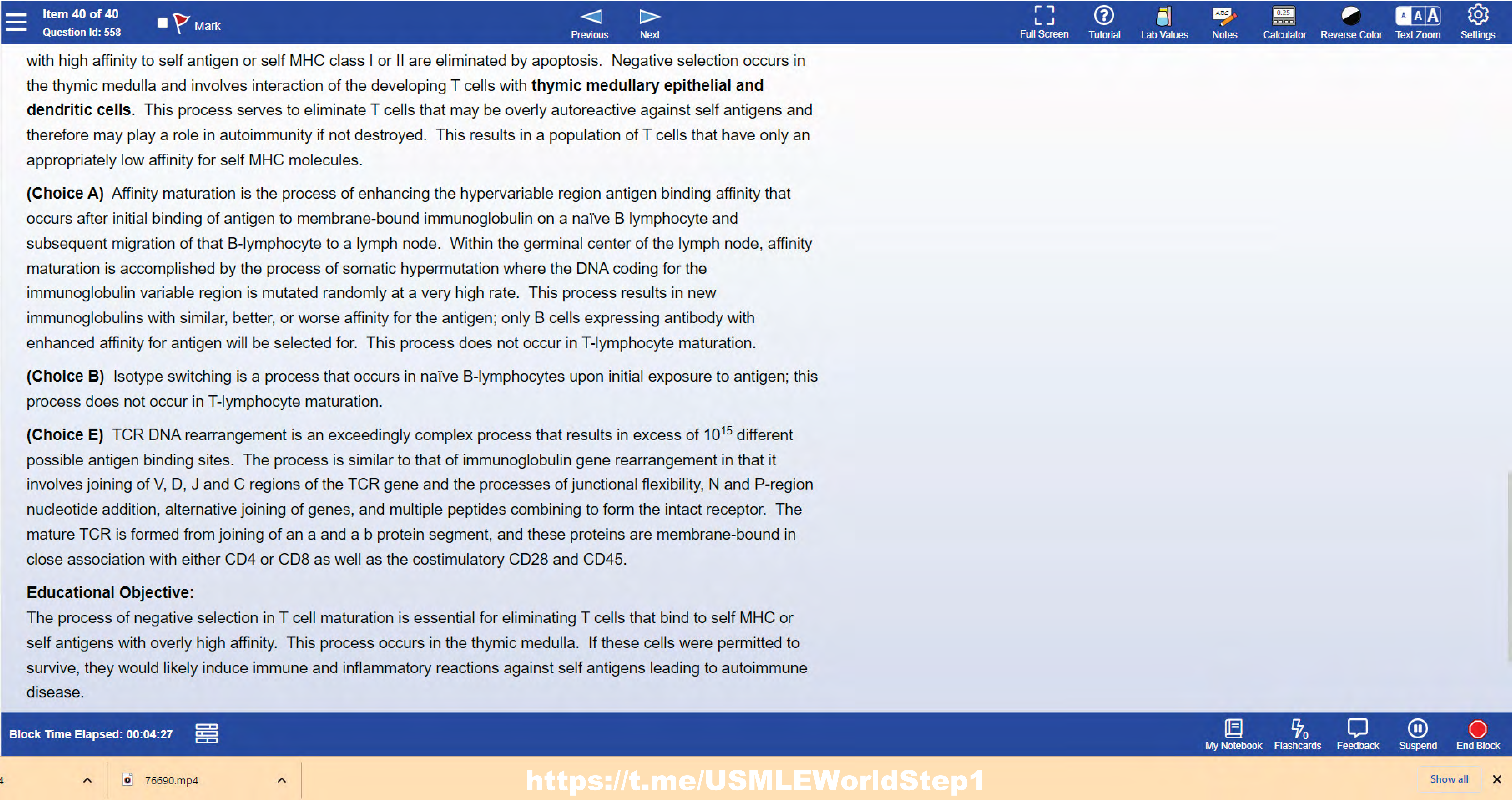

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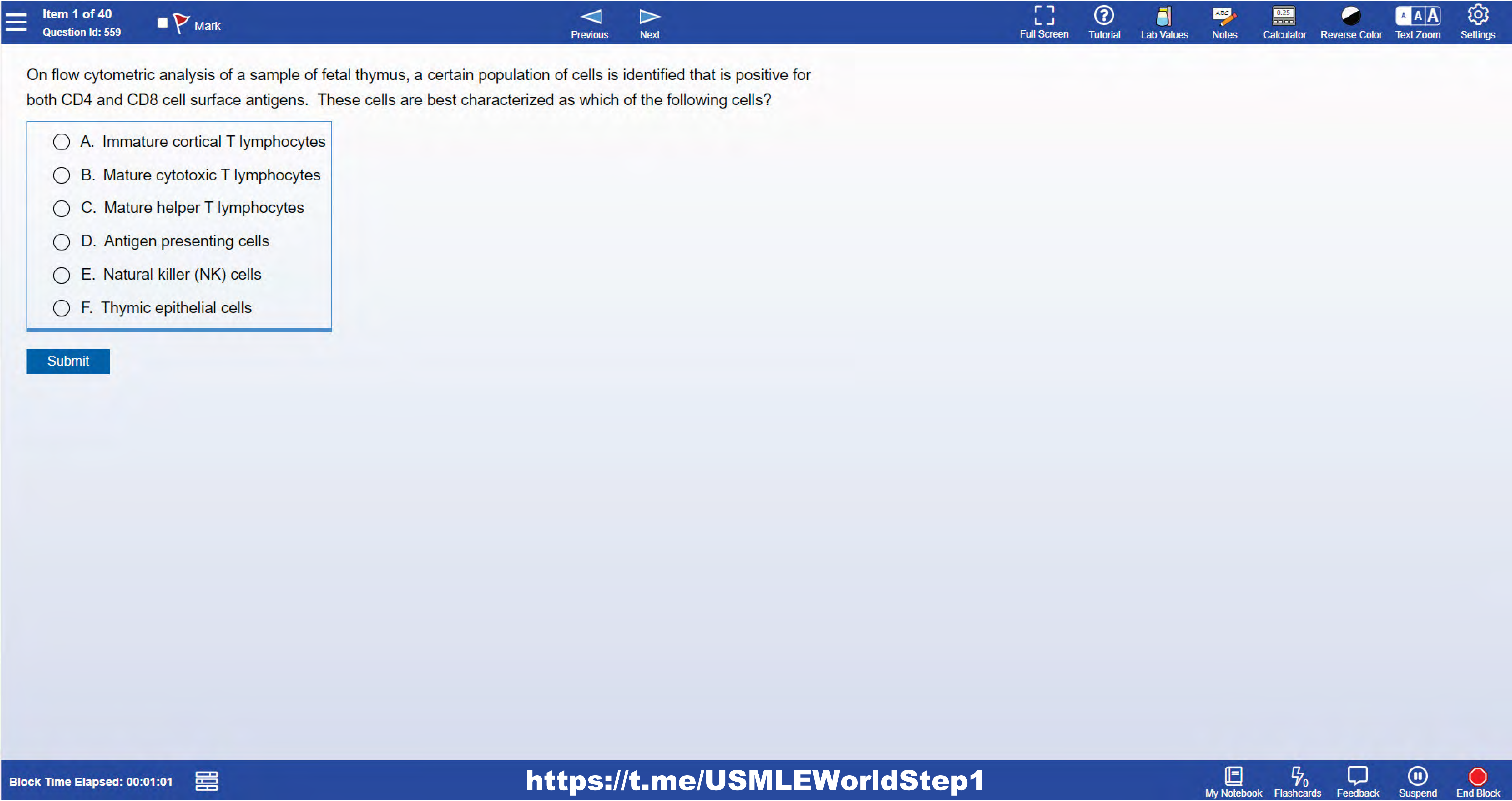
(Choice B) Isotype switching is a process that occurs in naïve B-lymphocytes upon initial exposure to antigen; this process does not occur in T-lymphocyte maturation.

(Choice E) TCR DNA rearrangement is an exceedingly complex process that results in excess of 10^{15} different possible antigen binding sites. The process is similar to that of immunoglobulin gene rearrangement in that it involves joining of V, D, J and C regions of the TCR gene and the processes of junctional flexibility, N and P-region nucleotide addition, alternative joining of genes, and multiple peptides combining to form the intact receptor. The mature TCR is formed from joining of an a and a b protein segment, and these proteins are membrane-bound in close association with either CD4 or CD8 as well as the costimulatory CD28 and CD45.

Educational Objective:

The process of negative selection in T cell maturation is essential for eliminating T cells that bind to self MHC or self antigens with overly high affinity. This process occurs in the thymic medulla. If these cells were permitted to survive, they would likely induce immune and inflammatory reactions against self antigens leading to autoimmune disease.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On flow cytometric analysis of a sample of fetal thymus, a certain population of cells is identified that is positive for both CD4 and CD8 cell surface antigens. These cells are best characterized as which of the following cells?

○ A. Immature cortical T lymphocytes
○ B. Mature cytotoxic T lymphocytes
○ C. Mature helper T lymphocytes
○ D. Antigen presenting cells
○ E. Natural killer (NK) cells
○ F. Thymic epithelial cells

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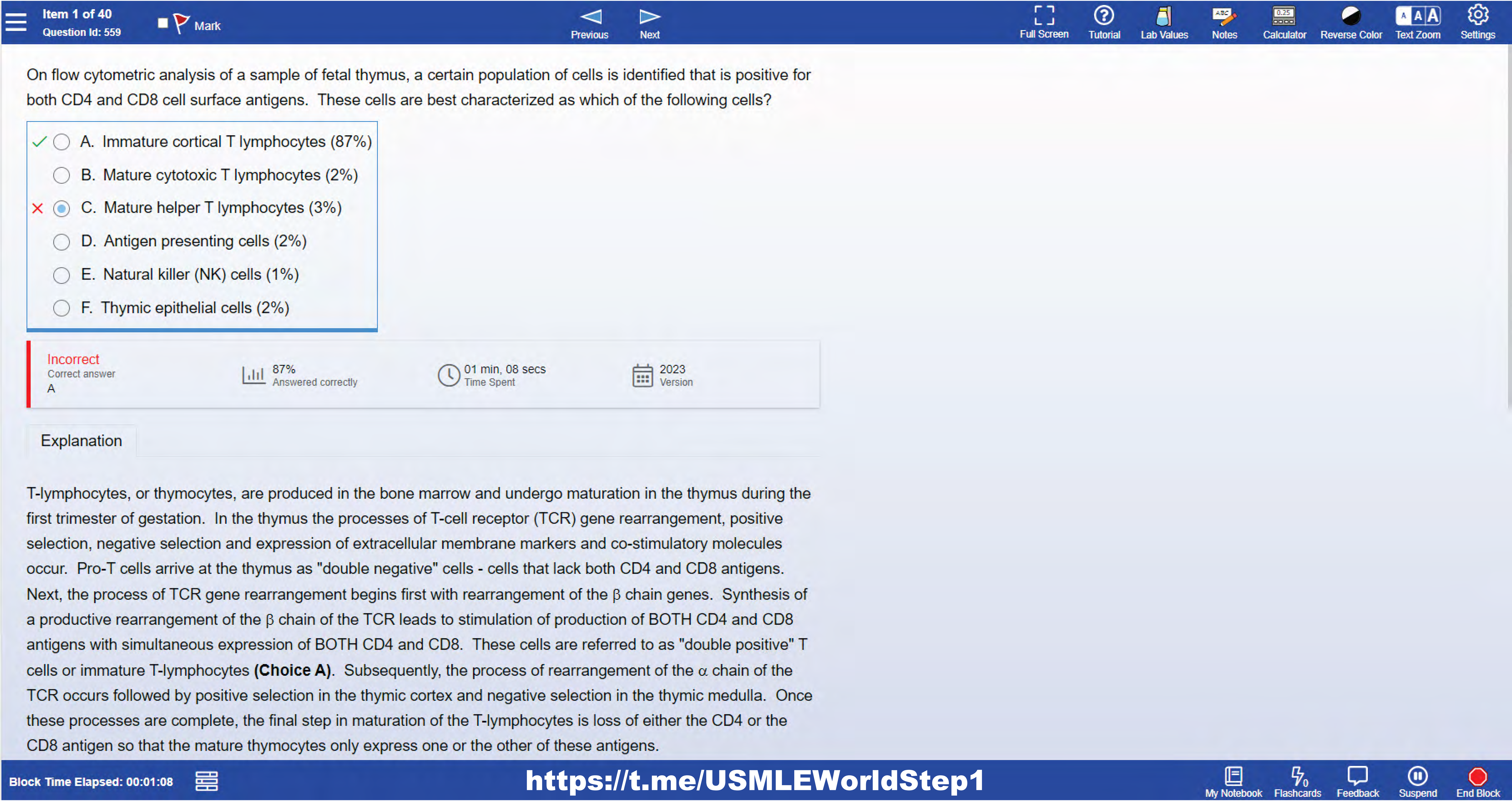
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On flow cytometric analysis of a sample of fetal thymus, a certain population of cells is identified that is positive for both CD4 and CD8 cell surface antigens. These cells are best characterized as which of the following cells?

- ✓ ○ A. Immature cortical T lymphocytes (87%)
- ○ B. Mature cytotoxic T lymphocytes (2%)
- ✗ ● C. Mature helper T lymphocytes (3%)
- ○ D. Antigen presenting cells (2%)
- ○ E. Natural killer (NK) cells (1%)
- ○ F. Thymic epithelial cells (2%)

Incorrect
Correct answer
A

87%
Answered correctly

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Explanation

T-lymphocytes, or thymocytes, are produced in the bone marrow and undergo maturation in the thymus during the first trimester of gestation. In the thymus the processes of T-cell receptor (TCR) gene rearrangement, positive selection, negative selection and expression of extracellular membrane markers and co-stimulatory molecules occur. Pro-T cells arrive at the thymus as "double negative" cells - cells that lack both CD4 and CD8 antigens. Next, the process of TCR gene rearrangement begins first with rearrangement of the β chain genes. Synthesis of a productive rearrangement of the β chain of the TCR leads to stimulation of production of BOTH CD4 and CD8 antigens with simultaneous expression of BOTH CD4 and CD8. These cells are referred to as "double positive" T cells or immature T-lymphocytes **(Choice A)**. Subsequently, the process of rearrangement of the α chain of the TCR occurs followed by positive selection in the thymic cortex and negative selection in the thymic medulla. Once these processes are complete, the final step in maturation of the T-lymphocytes is loss of either the CD4 or the CD8 antigen so that the mature thymocytes only express one or the other of these antigens.

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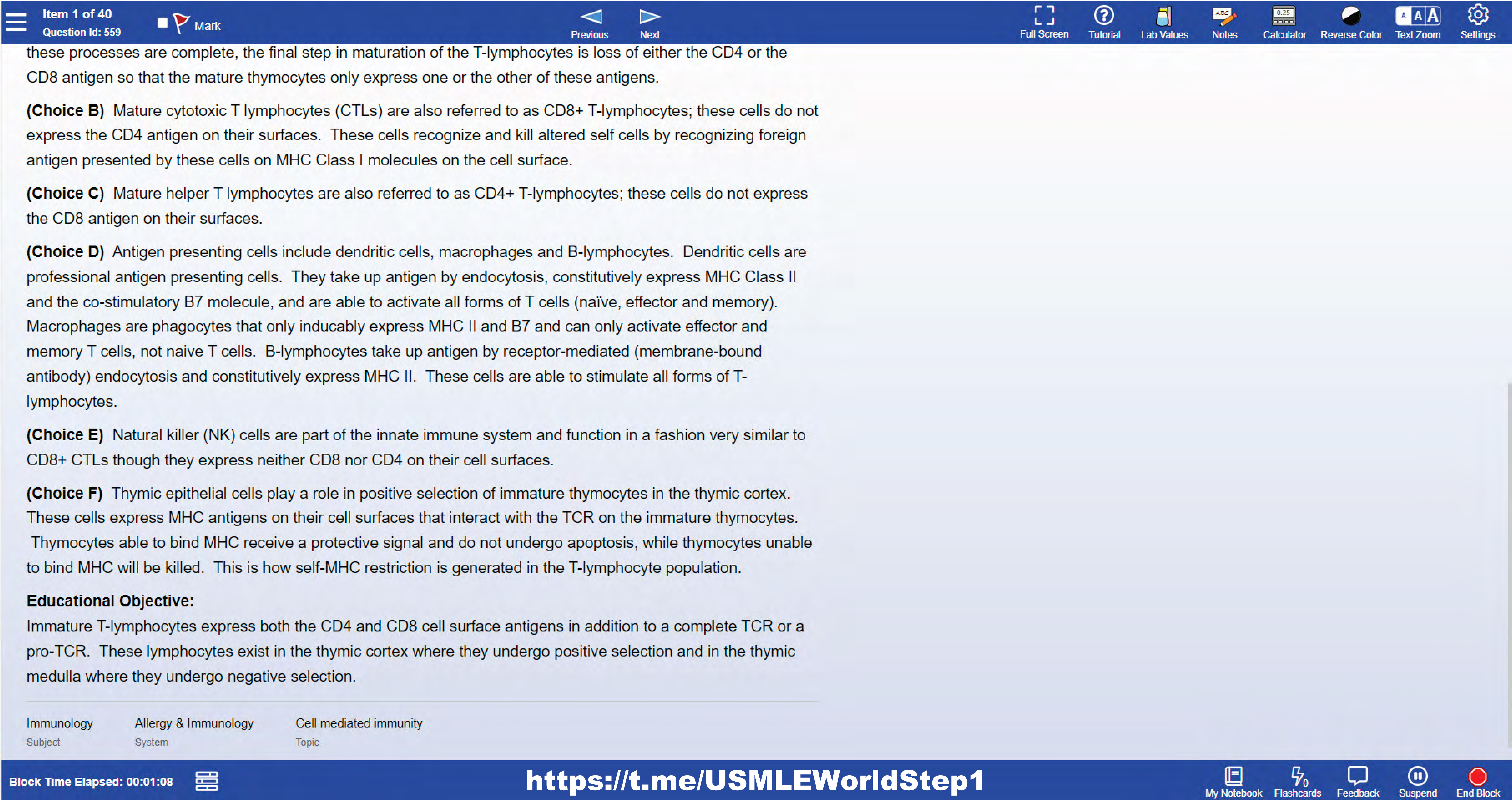
(Choice B) Mature cytotoxic T lymphocytes (CTLs) are also referred to as CD8+ T-lymphocytes; these cells do not express the CD4 antigen on their surfaces. These cells recognize and kill altered self cells by recognizing foreign antigen presented by these cells on MHC Class I molecules on the cell surface.

(Choice C) Mature helper T lymphocytes are also referred to as CD4+ T-lymphocytes; these cells do not express the CD8 antigen on their surfaces.

(Choice D) Antigen presenting cells include dendritic cells, macrophages and B-lymphocytes. Dendritic cells are professional antigen presenting cells. They take up antigen by endocytosis, constitutively express MHC Class II and the co-stimulatory B7 molecule, and are able to activate all forms of T cells (naïve, effector and memory). Macrophages are phagocytes that only inducably express MHC II and B7 and can only activate effector and memory T cells, not naive T cells. B-lymphocytes take up antigen by receptor-mediated (membrane-bound antibody) endocytosis and constitutively express MHC II. These cells are able to stimulate all forms of T-lymphocytes.

(Choice E) Natural killer (NK) cells are part of the innate immune system and function in a fashion very similar to CD8+ CTLs though they express neither CD8 nor CD4 on their cell surfaces.

(Choice F) Thymic epithelial cells play a role in positive selection of immature thymocytes in the thymic cortex.



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(Choice F) Thymic epithelial cells play a role in positive selection of immature thymocytes in the thymic cortex. These cells express MHC antigens on their cell surfaces that interact with the TCR on the immature thymocytes. Thymocytes able to bind MHC receive a protective signal and do not undergo apoptosis, while thymocytes unable to bind MHC will be killed. This is how self-MHC restriction is generated in the T-lymphocyte population.

Educational Objective:

Immature T-lymphocytes express both the CD4 and CD8 cell surface antigens in addition to a complete TCR or a pro-TCR. These lymphocytes exist in the thymic cortex where they undergo positive selection and in the thymic medulla where they undergo negative selection.

Immunology	Allergy & Immunology	Cell mediated immunity
Subject	System	Topic

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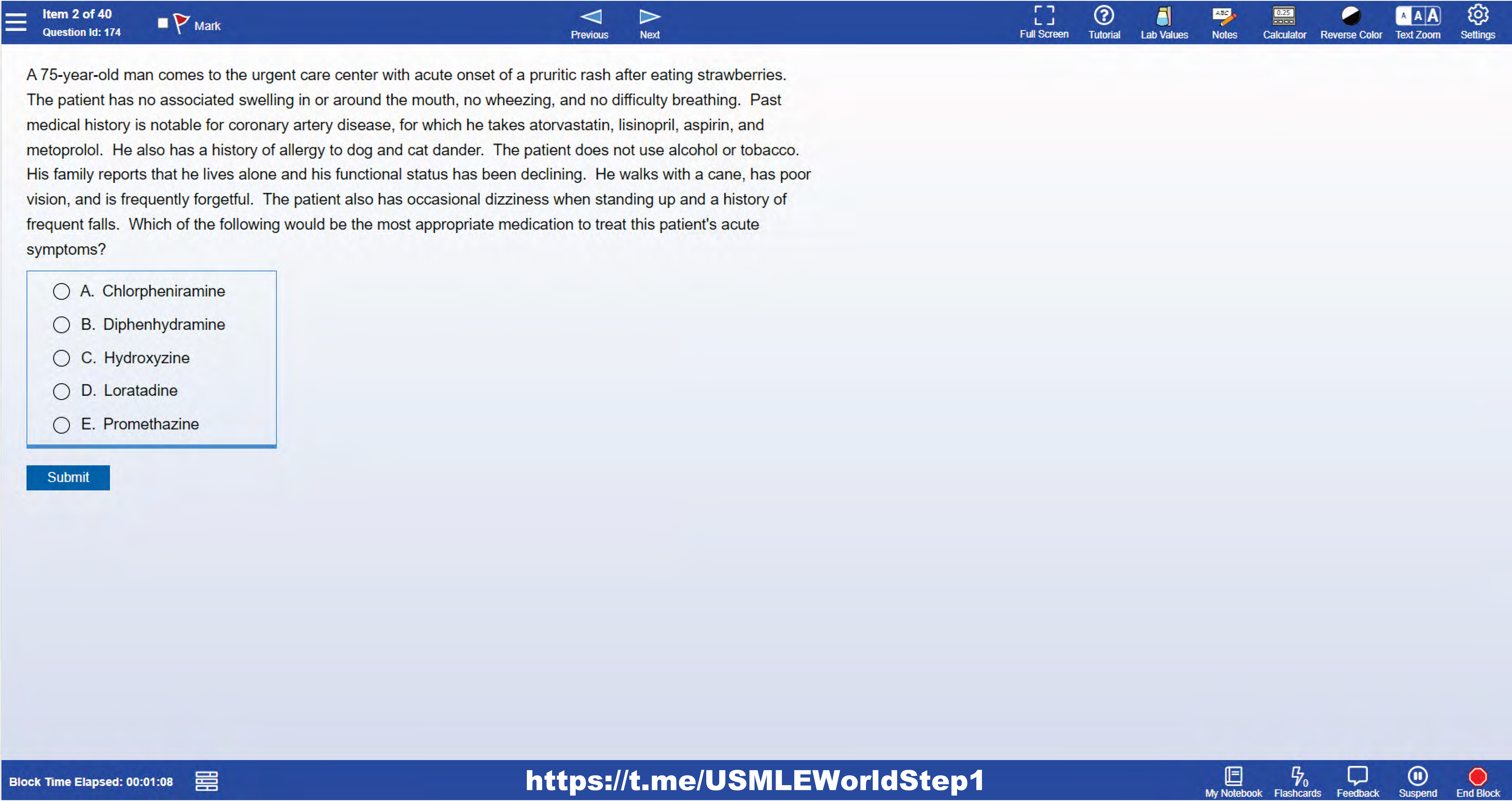
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A 75-year-old man comes to the urgent care center with acute onset of a pruritic rash after eating strawberries. The patient has no associated swelling in or around the mouth, no wheezing, and no difficulty breathing. Past medical history is notable for coronary artery disease, for which he takes atorvastatin, lisinopril, aspirin, and metoprolol. He also has a history of allergy to dog and cat dander. The patient does not use alcohol or tobacco. His family reports that he lives alone and his functional status has been declining. He walks with a cane, has poor vision, and is frequently forgetful. The patient also has occasional dizziness when standing up and a history of frequent falls. Which of the following would be the most appropriate medication to treat this patient's acute symptoms?

- ○ A. Chlorpheniramine
- ○ B. Diphenhydramine
- ○ C. Hydroxyzine
- ○ D. Loratadine
- ○ E. Promethazine

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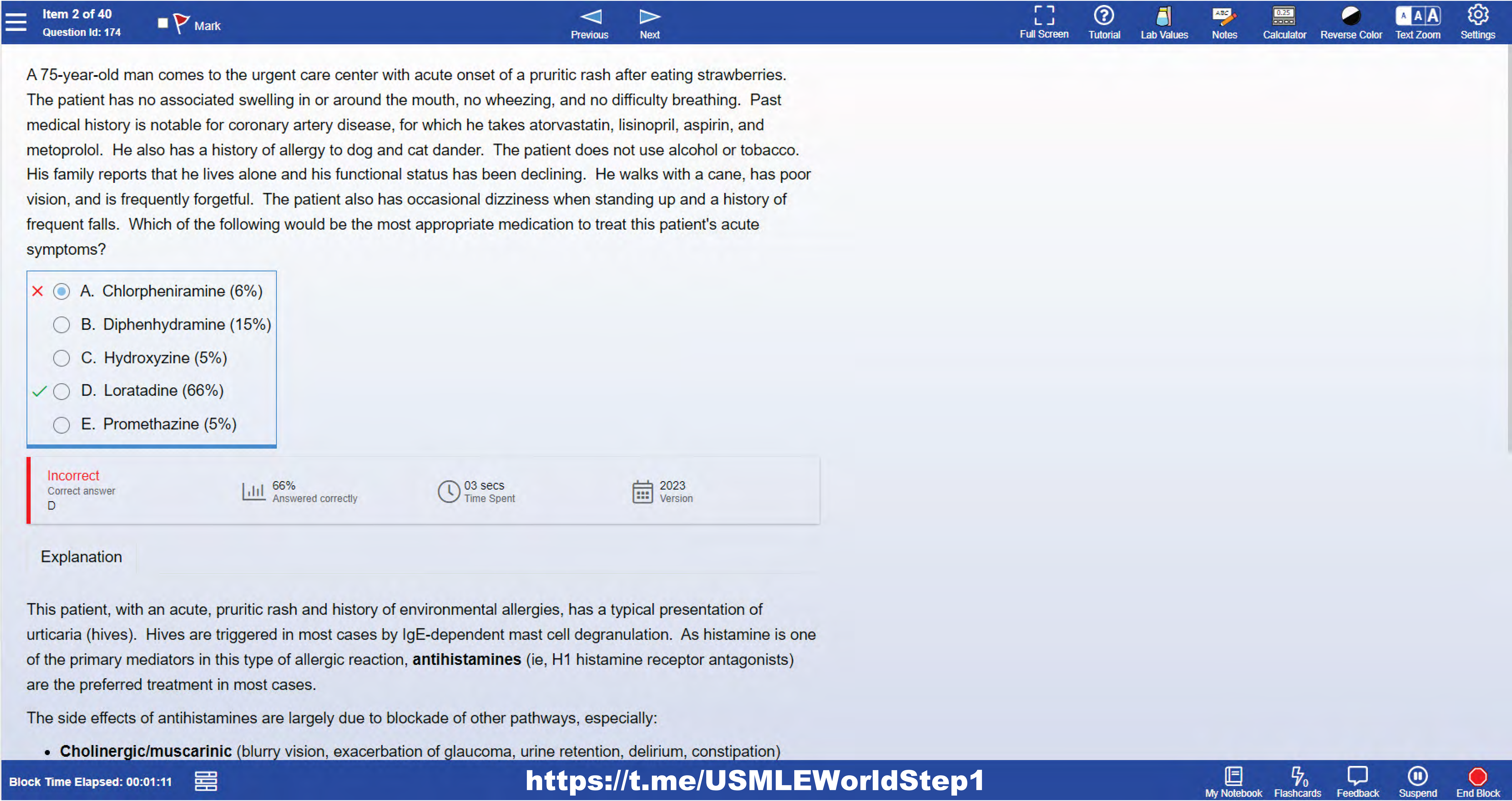
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✗ ● A. Chlorpheniramine (6%)
○ B. Diphenhydramine (15%)
○ C. Hydroxyzine (5%)
✓ ○ D. Loratadine (66%)
○ E. Promethazine (5%)

Incorrect
Correct answer
D

66%
Answered correctly

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Explanation

This patient, with an acute, pruritic rash and history of environmental allergies, has a typical presentation of urticaria (hives). Hives are triggered in most cases by IgE-dependent mast cell degranulation. As histamine is one of the primary mediators in this type of allergic reaction, **antihistamines** (ie, H1 histamine receptor antagonists) are the preferred treatment in most cases.

The side effects of antihistamines are largely due to blockade of other pathways, especially:

- **Cholinergic/muscarinic** (blurry vision, exacerbation of glaucoma, urine retention, delirium, constipation)

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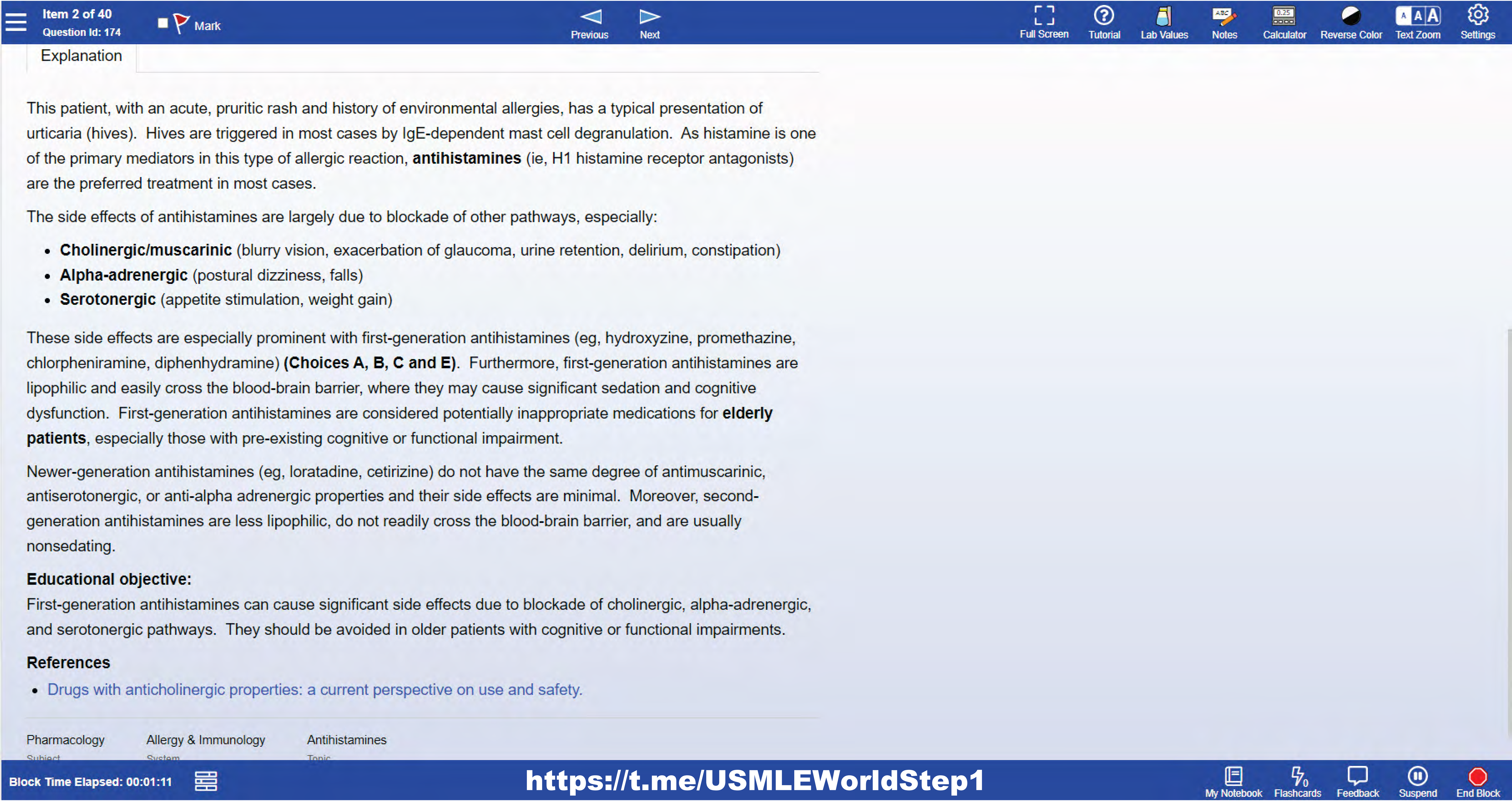
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Explanation

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The side effects of antihistamines are largely due to blockade of other pathways, especially:

- **Cholinergic/muscarinic** (blurry vision, exacerbation of glaucoma, urine retention, delirium, constipation)
- **Alpha-adrenergic** (postural dizziness, falls)
- **Serotonergic** (appetite stimulation, weight gain)

These side effects are especially prominent with first-generation antihistamines (eg, hydroxyzine, promethazine, chlorpheniramine, diphenhydramine) **(Choices A, B, C and E)**. Furthermore, first-generation antihistamines are lipophilic and easily cross the blood-brain barrier, where they may cause significant sedation and cognitive dysfunction. First-generation antihistamines are considered potentially inappropriate medications for **elderly patients**, especially those with pre-existing cognitive or functional impairment.

Newer-generation antihistamines (eg, loratadine, cetirizine) do not have the same degree of antimuscarinic, antiserotonergic, or anti-alpha adrenergic properties and their side effects are minimal. Moreover, second-generation antihistamines are less lipophilic, do not readily cross the blood-brain barrier, and are usually nonsedating.

Educational objective:
First-generation antihistamines can cause significant side effects due to blockade of cholinergic, alpha-adrenergic, and serotonergic pathways. They should be avoided in older patients with cognitive or functional impairments.

References

- Drugs with anticholinergic properties: a current perspective on use and safety.

Pharmacology
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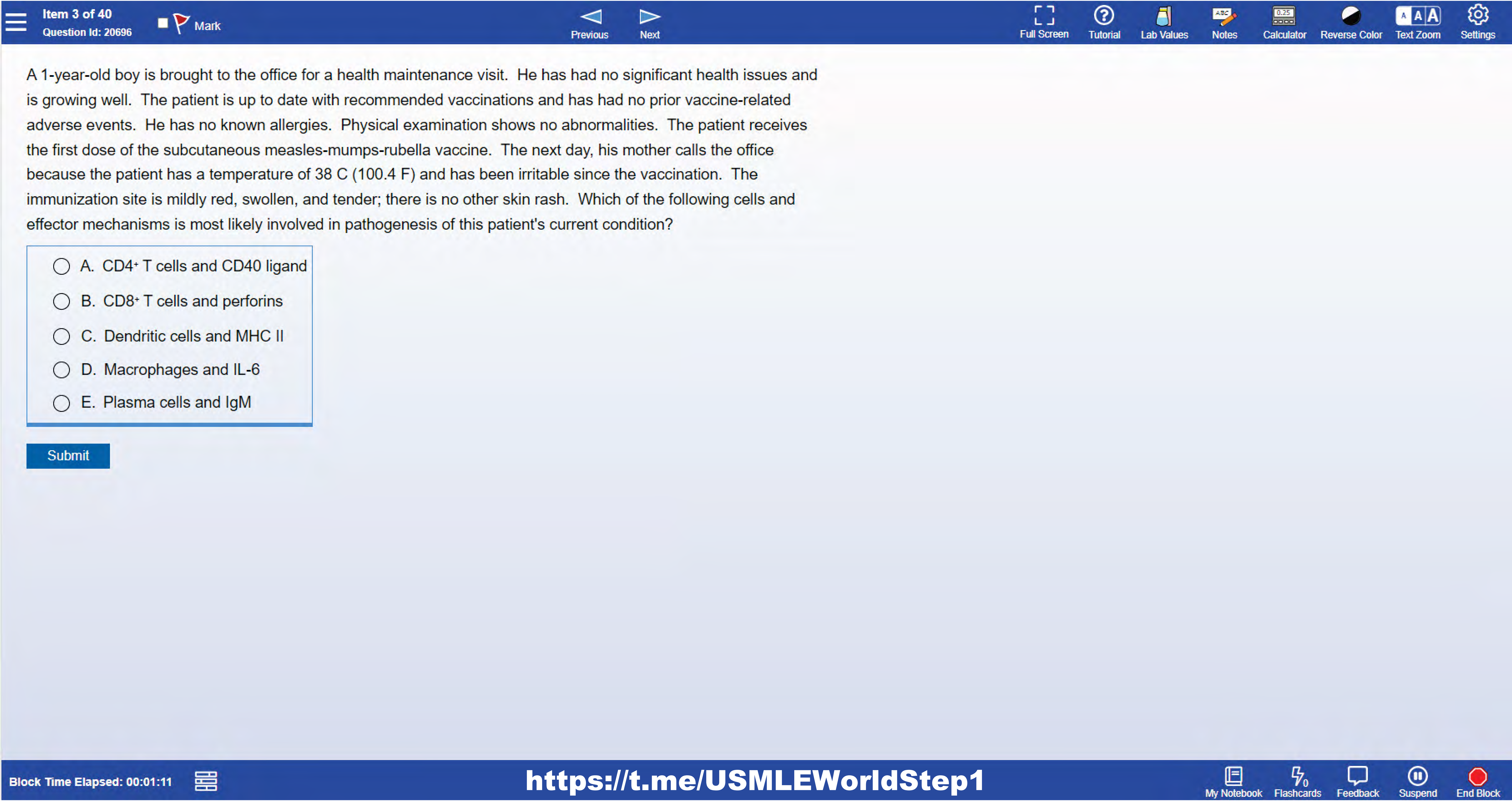
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A 1-year-old boy is brought to the office for a health maintenance visit. He has had no significant health issues and is growing well. The patient is up to date with recommended vaccinations and has had no prior vaccine-related adverse events. He has no known allergies. Physical examination shows no abnormalities. The patient receives the first dose of the subcutaneous measles-mumps-rubella vaccine. The next day, his mother calls the office because the patient has a temperature of 38 C (100.4 F) and has been irritable since the vaccination. The immunization site is mildly red, swollen, and tender; there is no other skin rash. Which of the following cells and effector mechanisms is most likely involved in pathogenesis of this patient's current condition?

○ A. $CD4^+$ T cells and CD40 ligand
○ B. $CD8^+$ T cells and perforins
○ C. Dendritic cells and MHC II
○ D. Macrophages and IL-6
○ E. Plasma cells and IgM

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- ✗ ● A. $CD4^+$ T cells and CD40 ligand (16%)
- ○ B. $CD8^+$ T cells and perforins (16%)
- ○ C. Dendritic cells and MHC II (21%)
- ✓ ○ D. Macrophages and IL-6 (39%)
- ○ E. Plasma cells and IgM (6%)

Incorrect
Correct answer
D

39%
Answered correctly

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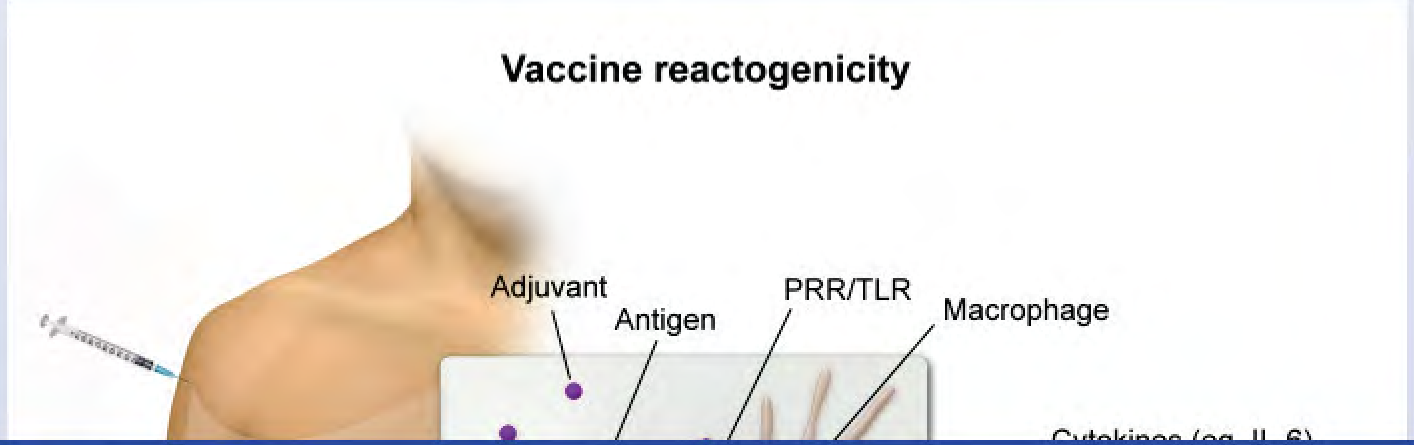
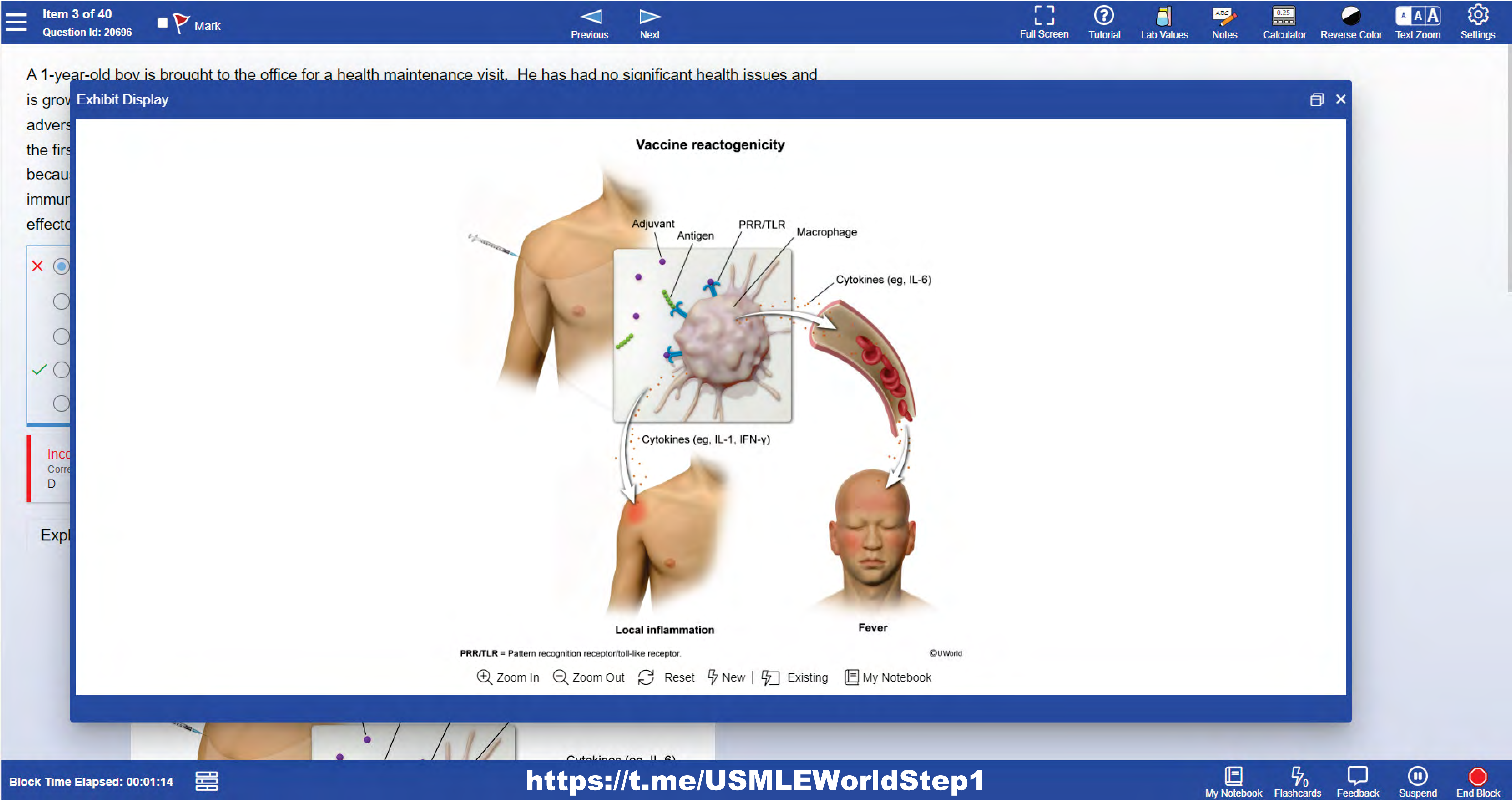
Explanation


Vaccine reactogenicity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Adjuvant
Antigen
PRR/TLR
Macrophage
Cytokines (eg, IL-6)
Cytokines (eg, IL-1, IFN-γ)
Local inflammation
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A 1-year-old boy is brought to the office for a health maintenance visit. He has had no significant health issues and

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Vaccine reactogenicity

PRR/TLR = Pattern recognition receptor/toll-like receptor.

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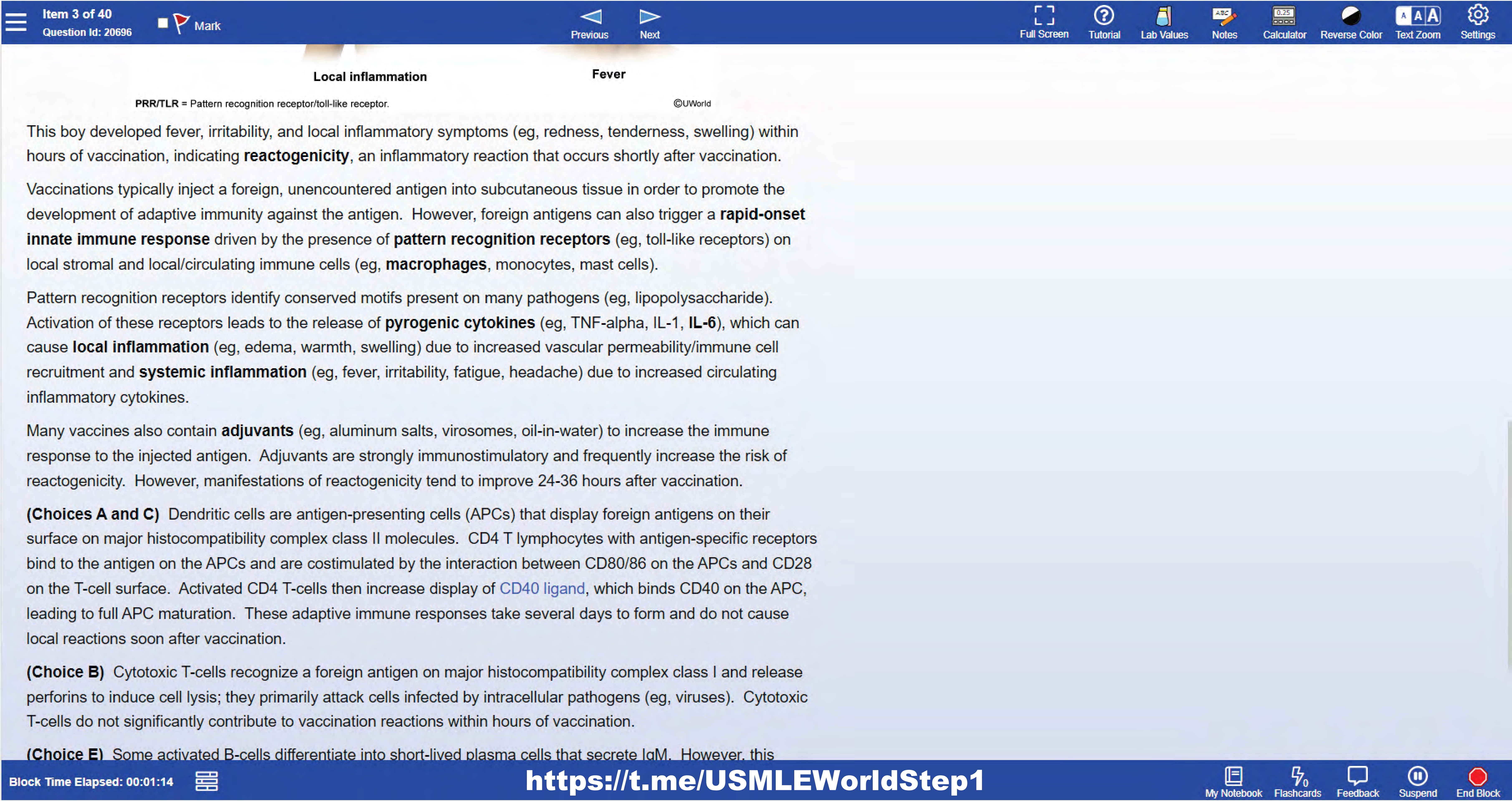


PRR/TLR = Pattern recognition receptor/toll-like receptor.

This boy developed fever, irritability, and local inflammatory symptoms (eg, redness, tenderness, swelling) within hours of vaccination, indicating **reactogenicity**, an inflammatory reaction that occurs shortly after vaccination.

Vaccinations typically inject a foreign, unencountered antigen into subcutaneous tissue in order to promote the development of adaptive immunity against the antigen. However, foreign antigens can also trigger a **rapid-onset innate immune response** driven by the presence of **pattern recognition receptors** (eg, toll-like receptors) on local stromal and local/circulating immune cells (eg, **macrophages**, monocytes, mast cells).

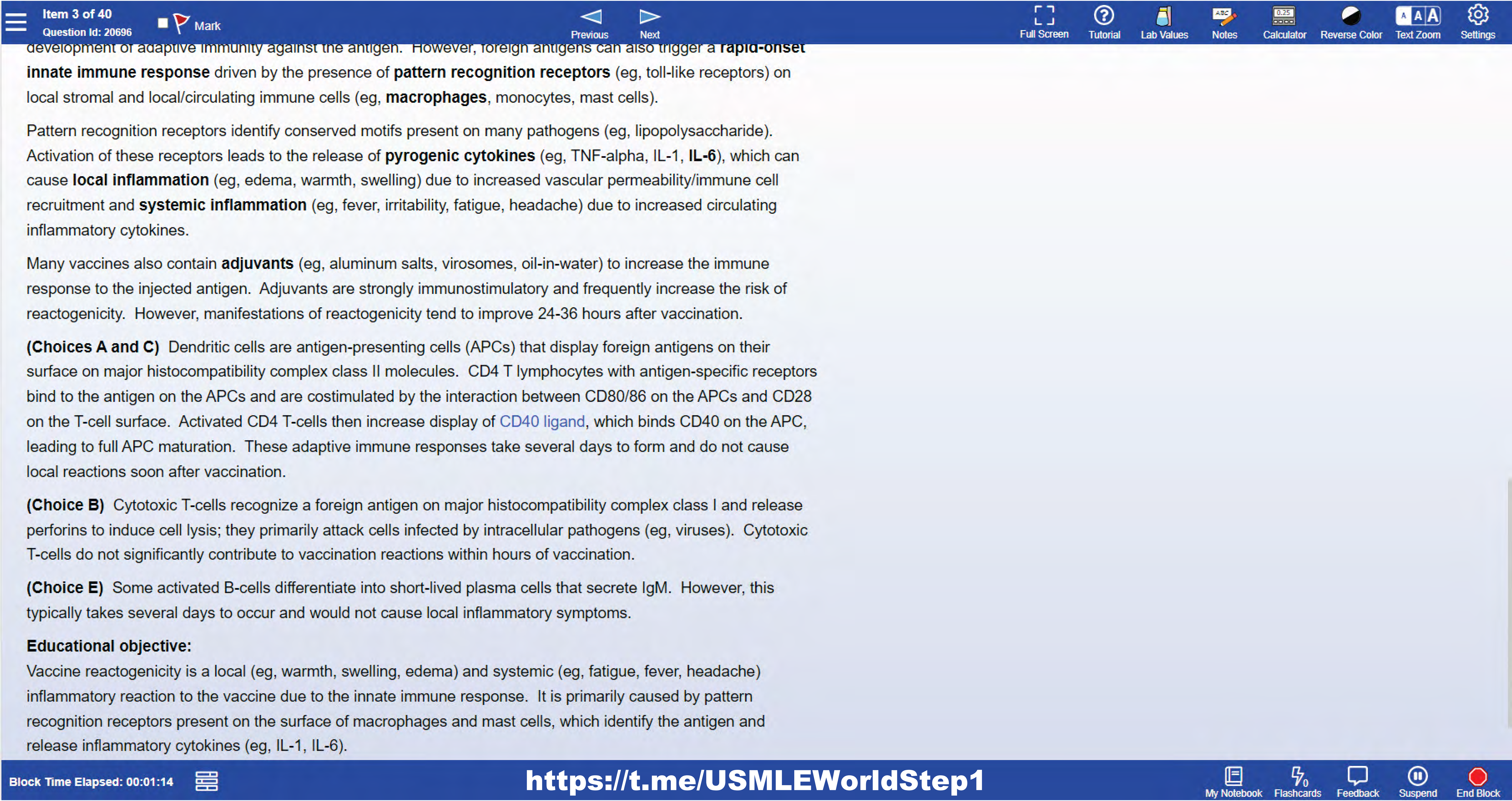
Pattern recognition receptors identify conserved motifs present on many pathogens (eg, lipopolysaccharide). Activation of these receptors leads to the release of **pyrogenic cytokines** (eg, TNF-alpha, IL-1, **IL-6**), which can cause **local inflammation** (eg, edema, warmth, swelling) due to increased vascular permeability/immune cell recruitment and **systemic inflammation** (eg, fever, irritability, fatigue, headache) due to increased circulating inflammatory cytokines.

Many vaccines also contain **adjuvants** (eg, aluminum salts, virosomes, oil-in-water) to increase the immune response to the injected antigen. Adjuvants are strongly immunostimulatory and frequently increase the risk of reactogenicity. However, manifestations of reactogenicity tend to improve 24-36 hours after vaccination.

(Choices A and C) Dendritic cells are antigen-presenting cells (APCs) that display foreign antigens on their surface on major histocompatibility complex class II molecules. CD4 T lymphocytes with antigen-specific receptors bind to the antigen on the APCs and are costimulated by the interaction between CD80/86 on the APCs and CD28 on the T-cell surface. Activated CD4 T-cells then increase display of CD40 ligand, which binds CD40 on the APC, leading to full APC maturation. These adaptive immune responses take several days to form and do not cause local reactions soon after vaccination.

(Choice B) Cytotoxic T-cells recognize a foreign antigen on major histocompatibility complex class I and release perforins to induce cell lysis; they primarily attack cells infected by intracellular pathogens (eg, viruses). Cytotoxic T-cells do not significantly contribute to vaccination reactions within hours of vaccination.

(Choice E) Some activated B-cells differentiate into short-lived plasma cells that secrete IgM. However, this



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(Choice E) Some activated B-cells differentiate into short-lived plasma cells that secrete IgM. However, this typically takes several days to occur and would not cause local inflammatory symptoms.

Educational objective:

Vaccine reactogenicity is a local (eg, warmth, swelling, edema) and systemic (eg, fatigue, fever, headache) inflammatory reaction to the vaccine due to the innate immune response. It is primarily caused by pattern recognition receptors present on the surface of macrophages and mast cells, which identify the antigen and release inflammatory cytokines (eg, IL-1, IL-6).

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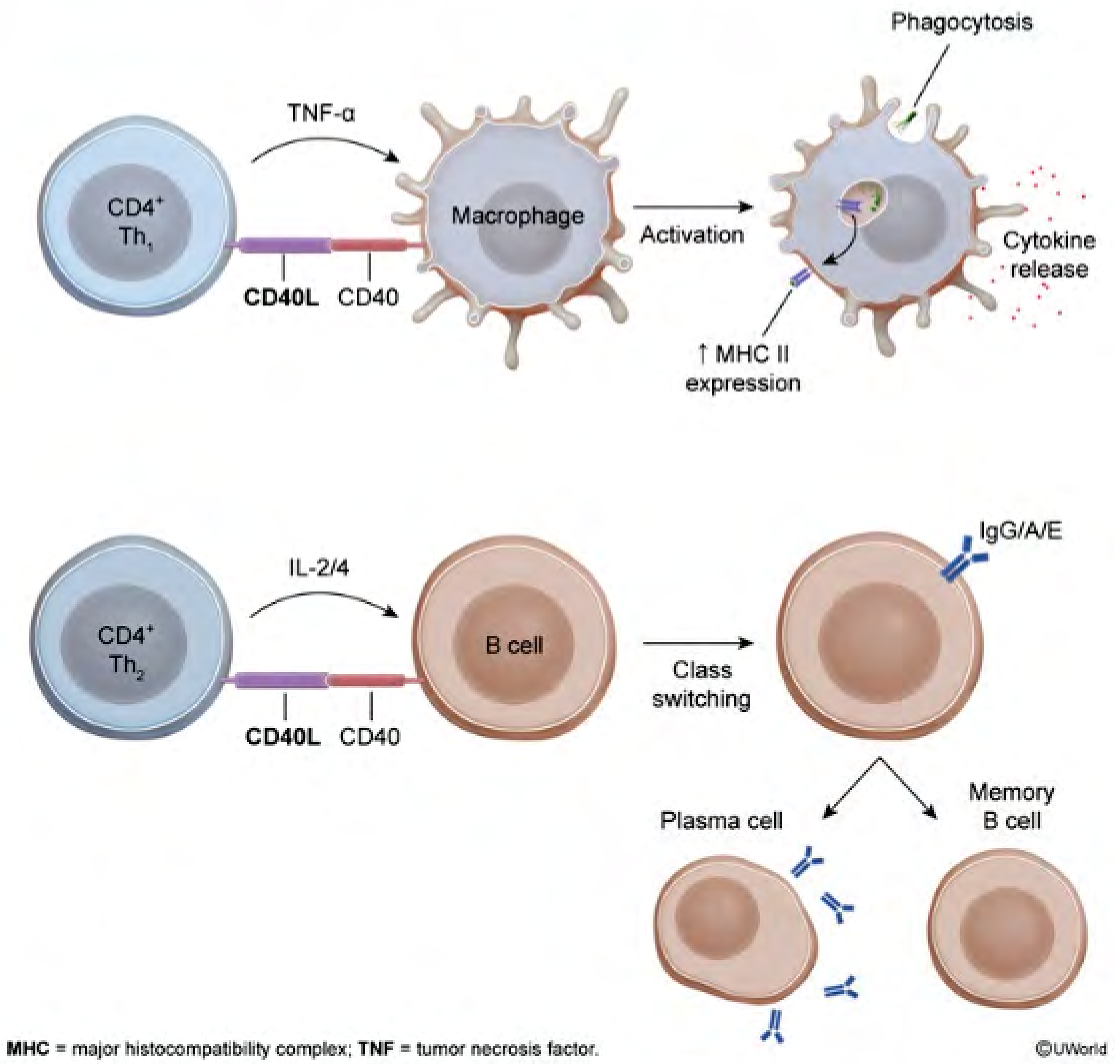
CD40-ligand activity


Phagocytosis
TNF-α
$CD4^+$ Th_1
Macrophage
Activation
Cytokine release
CD40L
CD40
↑ MHC II expression
IgG/A/E
IL-2/4
$CD4^+$ Th_2
B cell
Class switching
CD40L
CD40
Plasma cell
Memory B cell

MHC = major histocompatibility complex; **TNF** = tumor necrosis factor.

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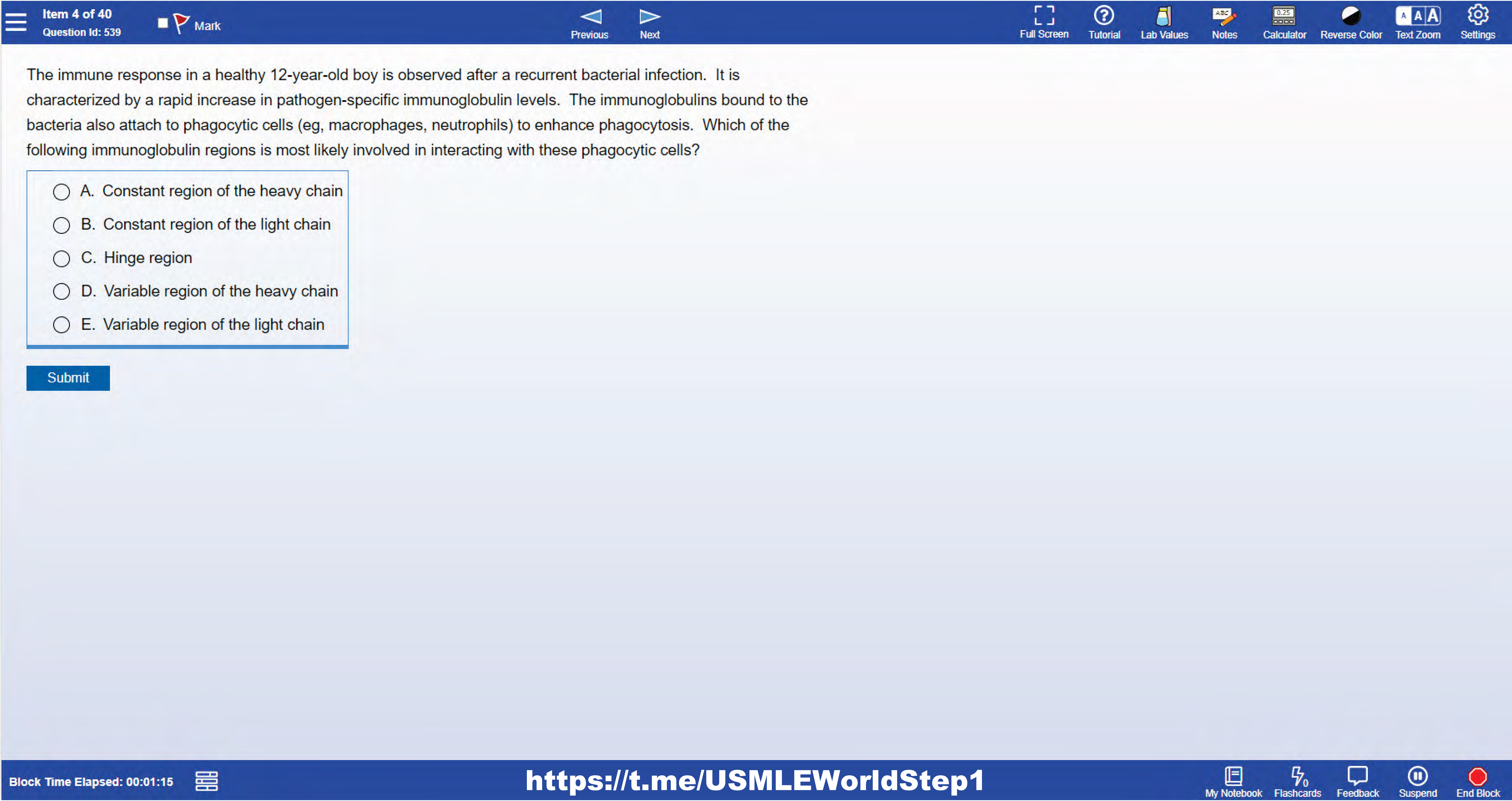
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The immune response in a healthy 12-year-old boy is observed after a recurrent bacterial infection. It is characterized by a rapid increase in pathogen-specific immunoglobulin levels. The immunoglobulins bound to the bacteria also attach to phagocytic cells (eg, macrophages, neutrophils) to enhance phagocytosis. Which of the following immunoglobulin regions is most likely involved in interacting with these phagocytic cells?

○ A. Constant region of the heavy chain
○ B. Constant region of the light chain
○ C. Hinge region
○ D. Variable region of the heavy chain
○ E. Variable region of the light chain

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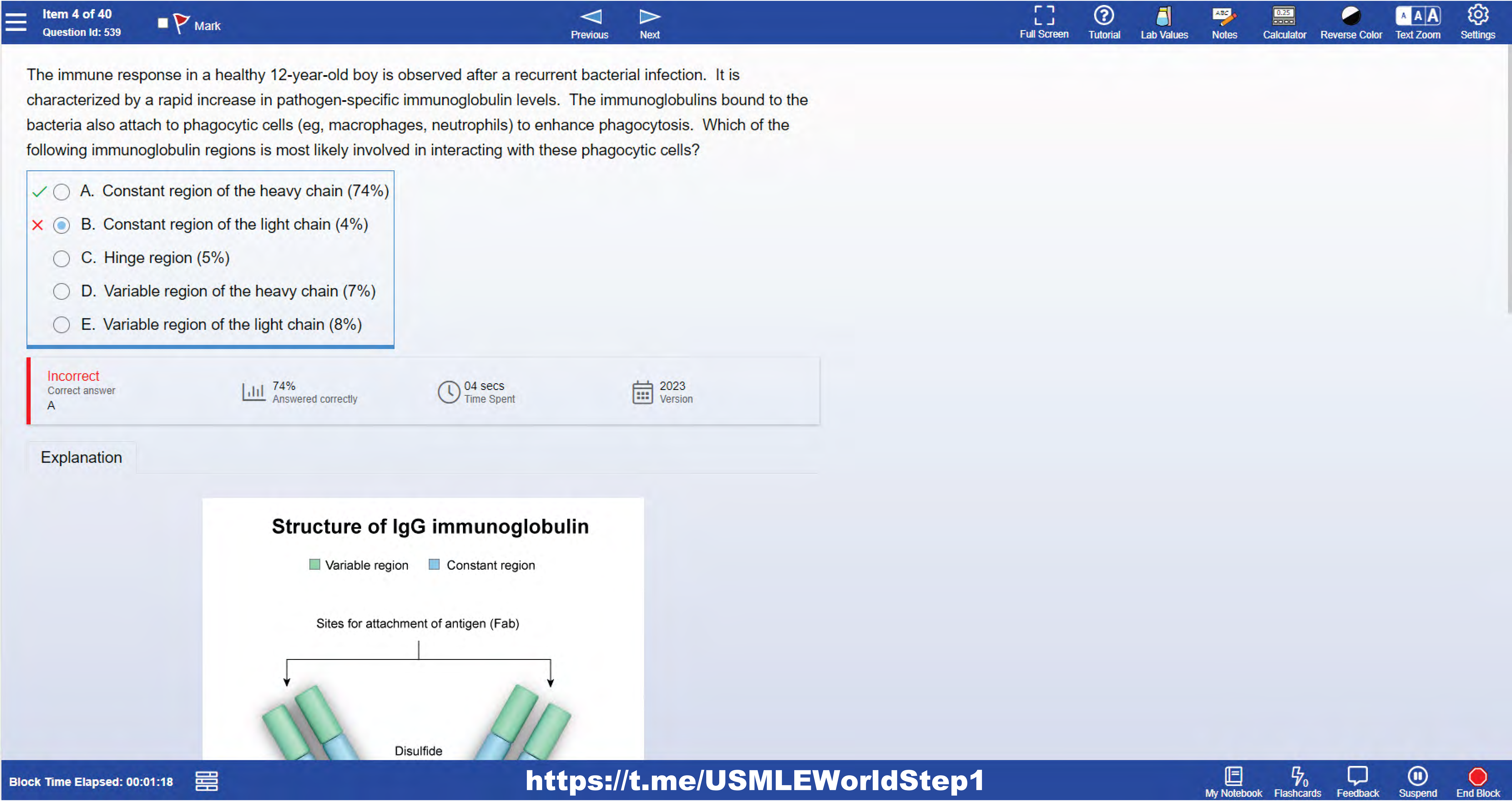
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- ✓ ○ A. Constant region of the heavy chain (74%)
- ✗ ● B. Constant region of the light chain (4%)
- ○ C. Hinge region (5%)
- ○ D. Variable region of the heavy chain (7%)
- ○ E. Variable region of the light chain (8%)

Incorrect
Correct answer
A

74%
Answered correctly

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Explanation

Structure of IgG immunoglobulin

🟩 Variable region 🟦 Constant region

Sites for attachment of antigen (Fab)
Disulfide

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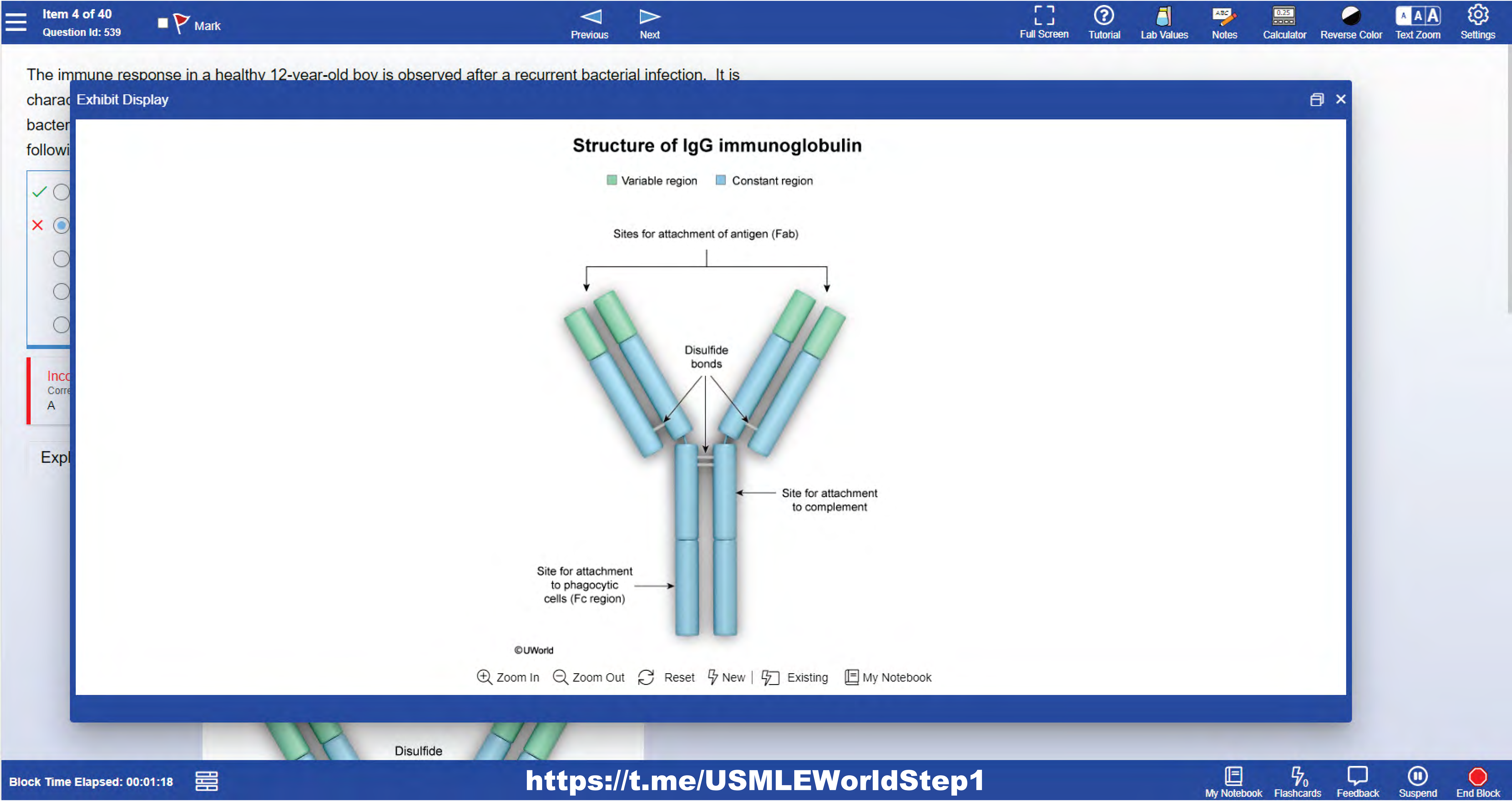
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Structure of IgG immunoglobulin

🟩 Variable region
🟦 Constant region
Sites for attachment of antigen (Fab)
Disulfide bonds
Site for attachment to complement
Site for attachment to phagocytic cells (Fc region)
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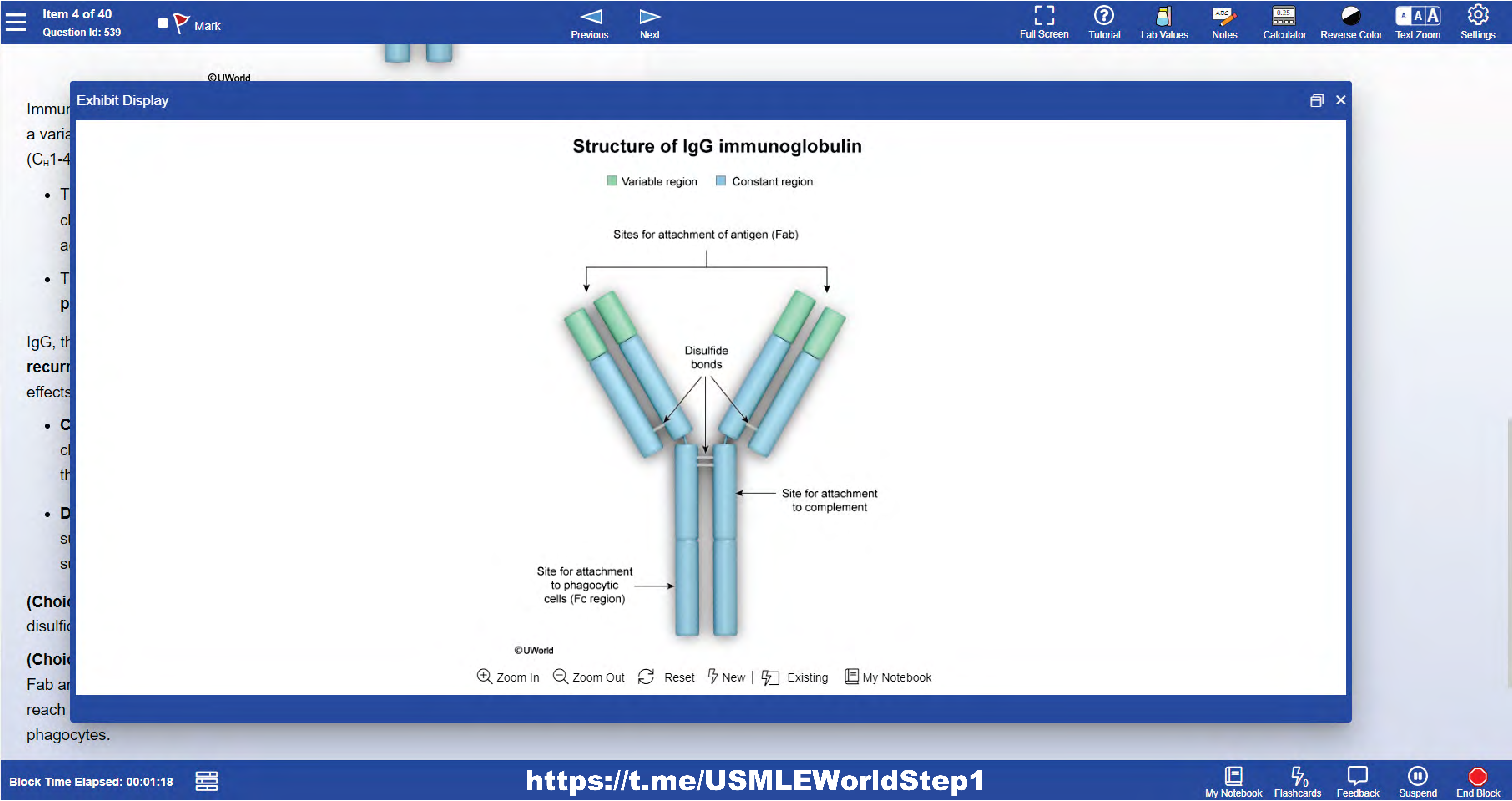
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Structure of IgG immunoglobulin

🟩 Variable region 🟦 Constant region

Sites for attachment of antigen (Fab)
Disulfide bonds
Site for attachment to complement
Site for attachment to phagocytic cells (Fc region)

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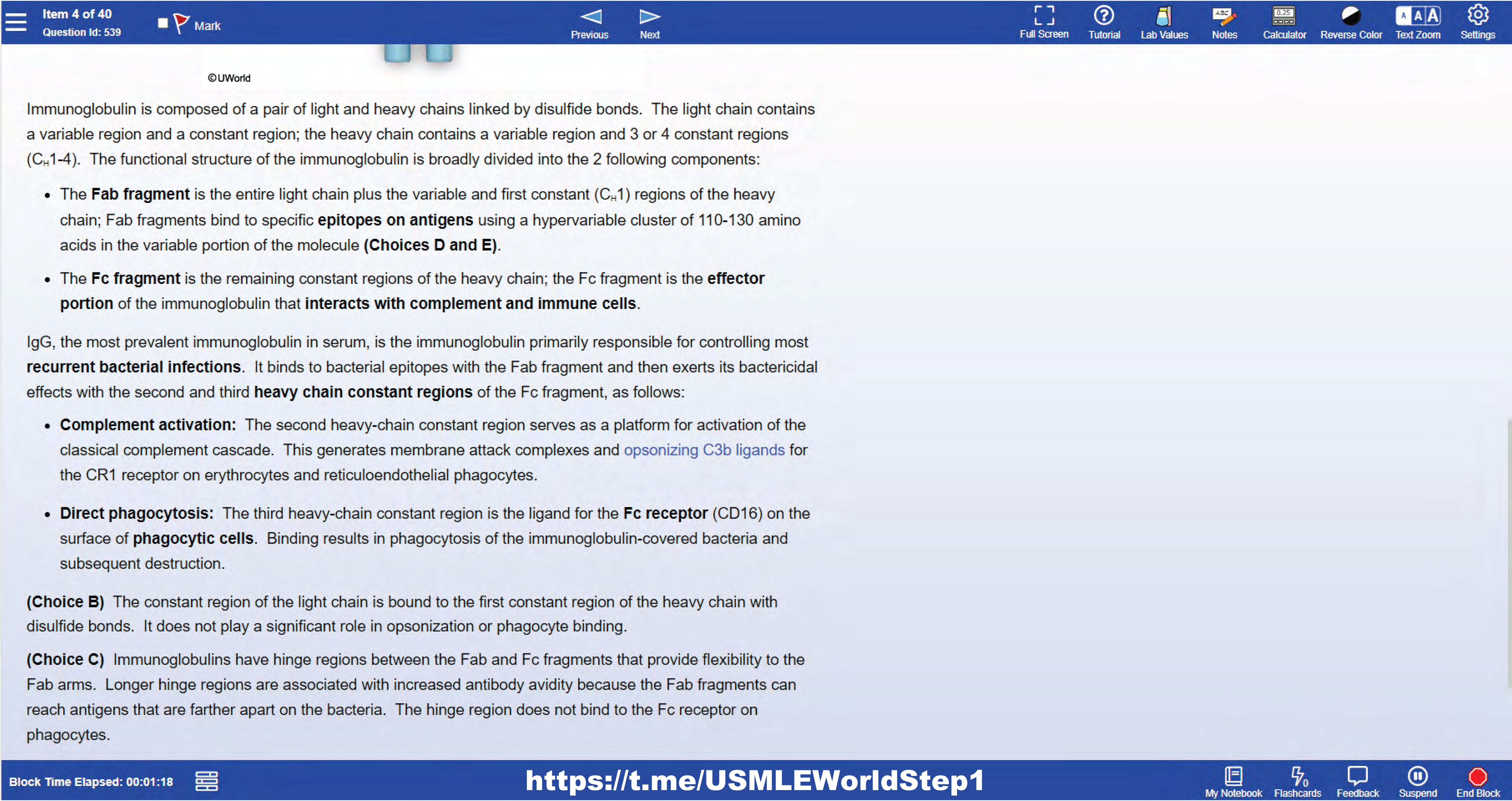

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Immunoglobulin is composed of a pair of light and heavy chains linked by disulfide bonds. The light chain contains a variable region and a constant region; the heavy chain contains a variable region and 3 or 4 constant regions (C_H1-4). The functional structure of the immunoglobulin is broadly divided into the 2 following components:

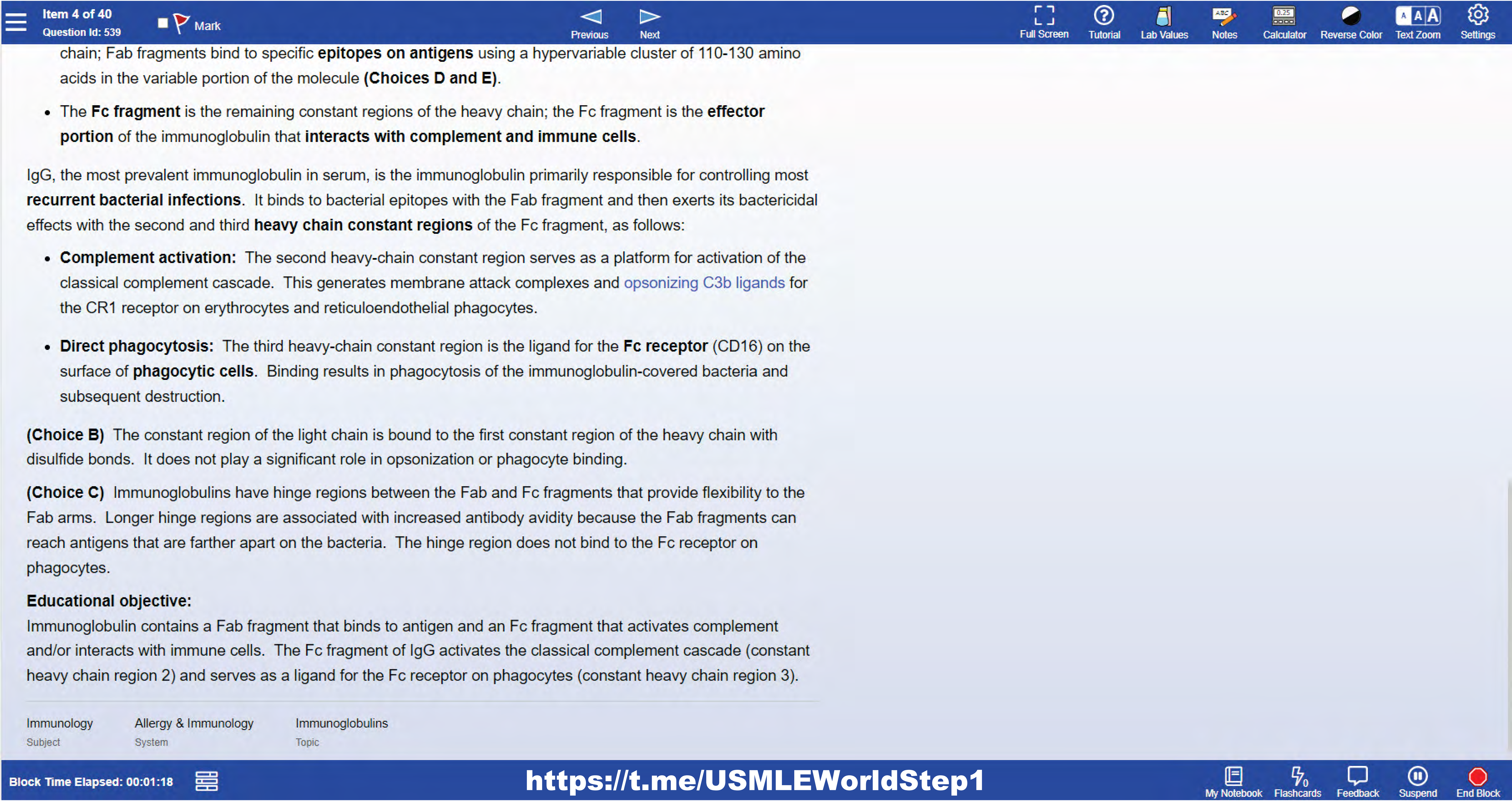
- The **Fab fragment** is the entire light chain plus the variable and first constant (C_H1) regions of the heavy chain; Fab fragments bind to specific **epitopes on antigens** using a hypervariable cluster of 110-130 amino acids in the variable portion of the molecule **(Choices D and E)**.
- The **Fc fragment** is the remaining constant regions of the heavy chain; the Fc fragment is the **effector portion** of the immunoglobulin that **interacts with complement and immune cells**.

IgG, the most prevalent immunoglobulin in serum, is the immunoglobulin primarily responsible for controlling most **recurrent bacterial infections**. It binds to bacterial epitopes with the Fab fragment and then exerts its bactericidal effects with the second and third **heavy chain constant regions** of the Fc fragment, as follows:

- **Complement activation:** The second heavy-chain constant region serves as a platform for activation of the classical complement cascade. This generates membrane attack complexes and opsonizing C3b ligands for the CR1 receptor on erythrocytes and reticuloendothelial phagocytes.
- **Direct phagocytosis:** The third heavy-chain constant region is the ligand for the **Fc receptor** (CD16) on the surface of **phagocytic cells**. Binding results in phagocytosis of the immunoglobulin-covered bacteria and subsequent destruction.

(Choice B) The constant region of the light chain is bound to the first constant region of the heavy chain with disulfide bonds. It does not play a significant role in opsonization or phagocyte binding.

(Choice C) Immunoglobulins have hinge regions between the Fab and Fc fragments that provide flexibility to the Fab arms. Longer hinge regions are associated with increased antibody avidity because the Fab fragments can reach antigens that are farther apart on the bacteria. The hinge region does not bind to the Fc receptor on phagocytes.



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chain; Fab fragments bind to specific **epitopes on antigens** using a hypervariable cluster of 110-130 amino acids in the variable portion of the molecule **(Choices D and E)**.

- The **Fc fragment** is the remaining constant regions of the heavy chain; the Fc fragment is the **effector portion** of the immunoglobulin that **interacts with complement and immune cells**.

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Educational objective:
Immunoglobulin contains a Fab fragment that binds to antigen and an Fc fragment that activates complement and/or interacts with immune cells. The Fc fragment of IgG activates the classical complement cascade (constant heavy chain region 2) and serves as a ligand for the Fc receptor on phagocytes (constant heavy chain region 3).

Immunology	Allergy & Immunology	Immunoglobulins
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chain; Fab fragments bind to specific **epitopes on antigens** using a hypervariable cluster of 110-130 amino

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heavy chain region 2) and serves as a ligand for the Fc receptor on phagocytes (constant heavy chain region 3).

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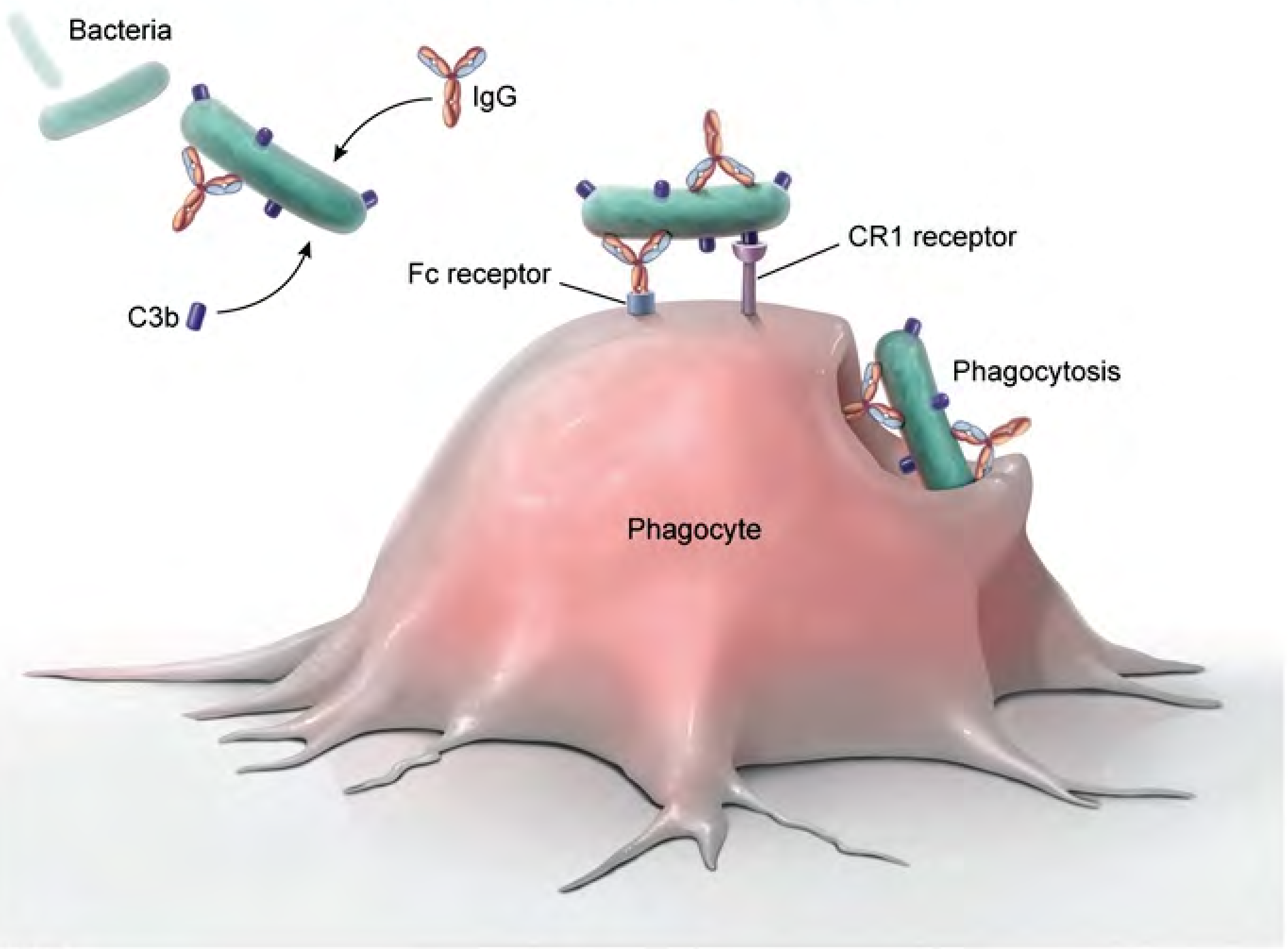
Opsonization & phagocytosis



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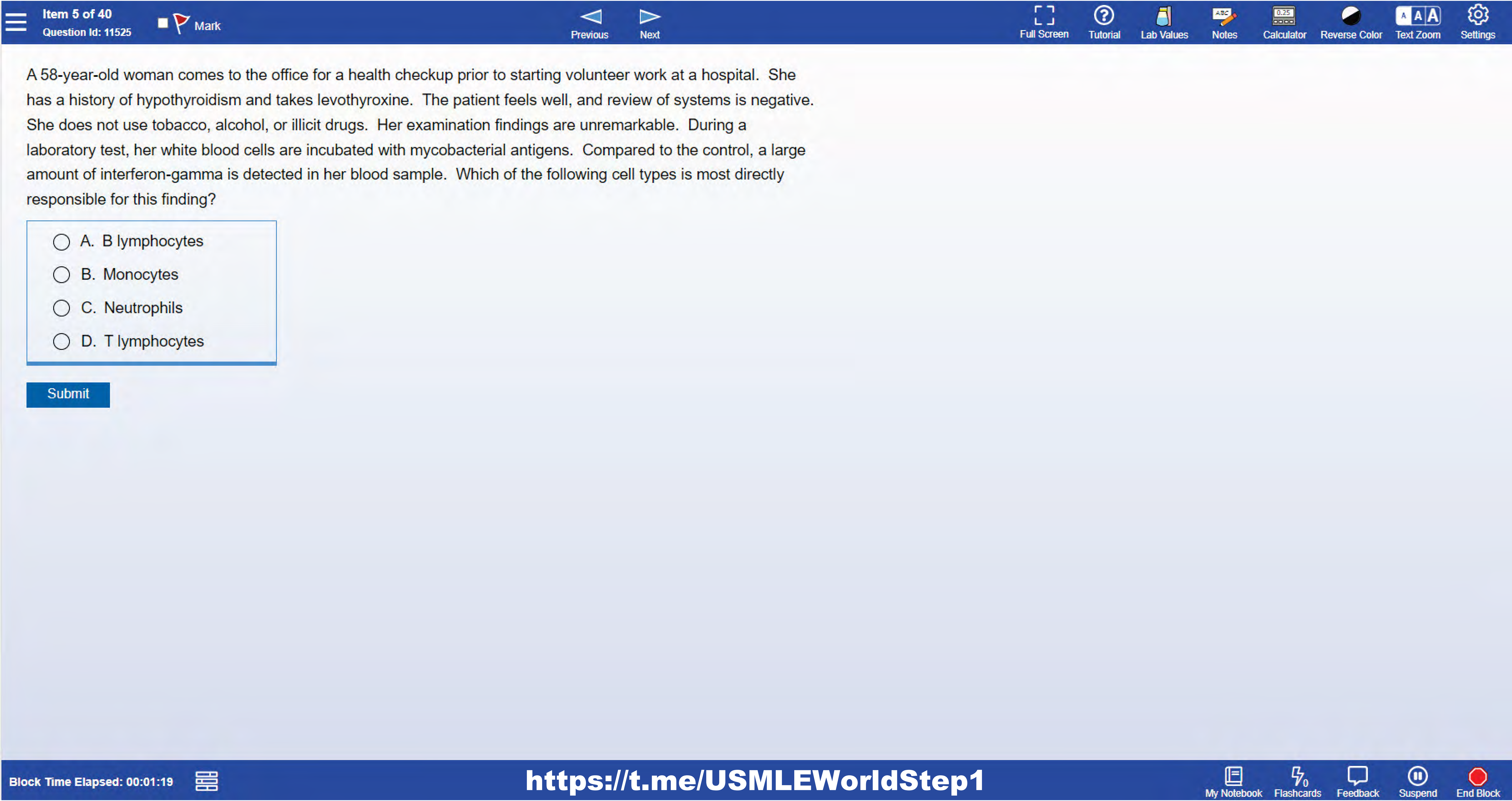
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A 58-year-old woman comes to the office for a health checkup prior to starting volunteer work at a hospital. She has a history of hypothyroidism and takes levothyroxine. The patient feels well, and review of systems is negative. She does not use tobacco, alcohol, or illicit drugs. Her examination findings are unremarkable. During a laboratory test, her white blood cells are incubated with mycobacterial antigens. Compared to the control, a large amount of interferon-gamma is detected in her blood sample. Which of the following cell types is most directly responsible for this finding?

○ A. B lymphocytes
○ B. Monocytes
○ C. Neutrophils
○ D. T lymphocytes

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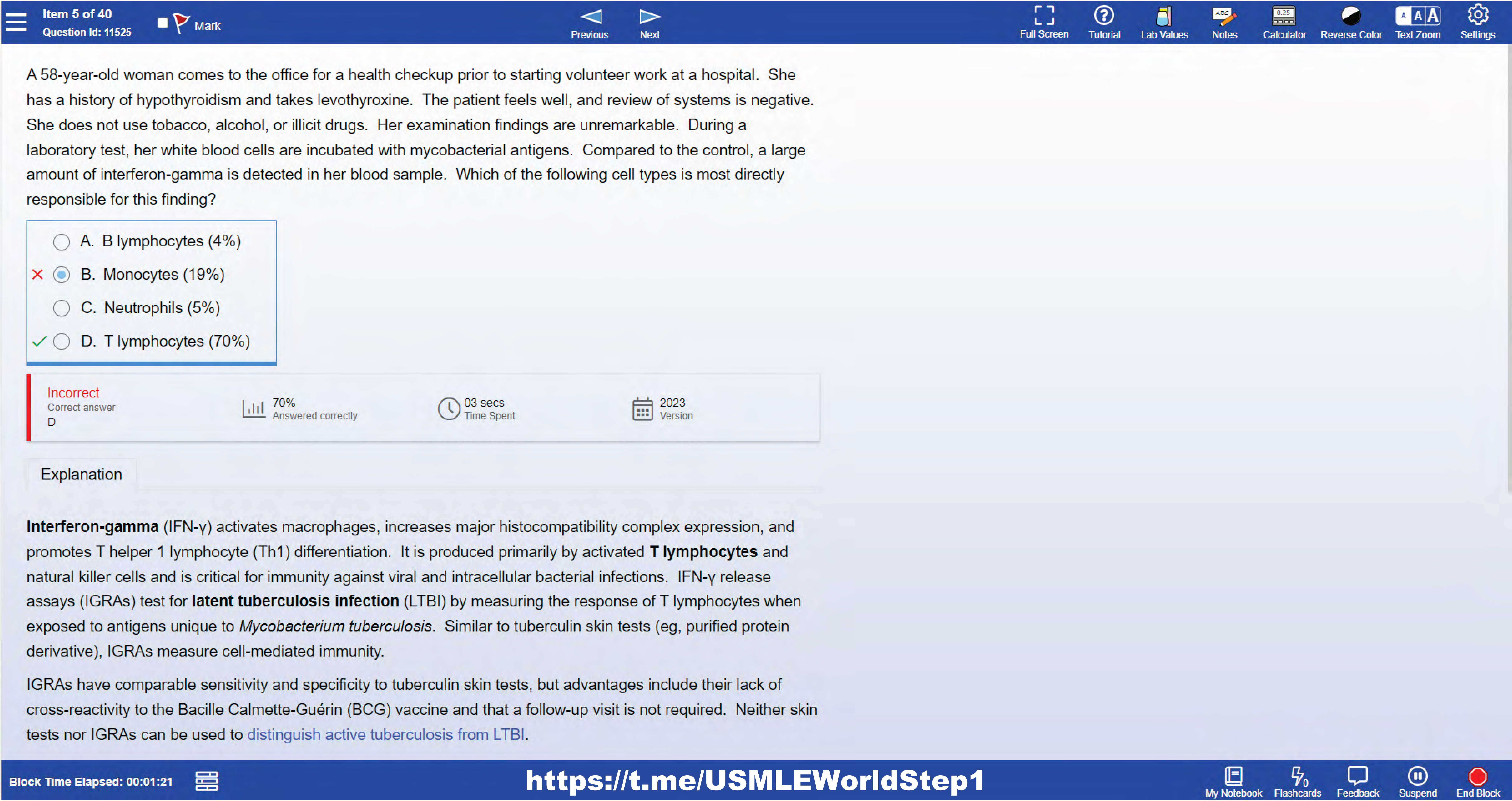
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Settings

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○ A. B lymphocytes (4%)

✗ ● B. Monocytes (19%)

○ C. Neutrophils (5%)

✓ ○ D. T lymphocytes (70%)

Incorrect
Correct answer
D

70%
Answered correctly

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Explanation

Interferon-gamma (IFN-γ) activates macrophages, increases major histocompatibility complex expression, and promotes T helper 1 lymphocyte (Th1) differentiation. It is produced primarily by activated **T lymphocytes** and natural killer cells and is critical for immunity against viral and intracellular bacterial infections. IFN-γ release assays (IGRAs) test for **latent tuberculosis infection** (LTBI) by measuring the response of T lymphocytes when exposed to antigens unique to *Mycobacterium tuberculosis*. Similar to tuberculin skin tests (eg, purified protein derivative), IGRAs measure cell-mediated immunity.

IGRAs have comparable sensitivity and specificity to tuberculin skin tests, but advantages include their lack of cross-reactivity to the Bacille Calmette-Guérin (BCG) vaccine and that a follow-up visit is not required. Neither skin tests nor IGRAs can be used to distinguish active tuberculosis from LTBI.

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Explanation

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(Choice A) B lymphocytes are the main cell type involved in the humoral immune system and the production of circulating antibodies.

(Choice B) Antigen-presenting cells such as monocyte-derived macrophages interact with T cells to control the immune response but are not directly responsible for IFN-γ release.

(Choice C) Neutrophils are involved in the phagocytosis of bacteria and other pathogens.

Educational objective:
Interferon-gamma (IFN-γ) release assays test for latent tuberculosis infection by measuring the amount of IFN-γ released by T lymphocytes when exposed to antigens unique to *Mycobacterium tuberculosis*.

References

- Gamma interferon release assays for detection of Mycobacterium tuberculosis infection.
- Clinical application and limitations of interferon-gamma release assays for the diagnosis of latent tuberculosis infection.

Immunology	Allergy & Immunology	Tuberculosis
Subject	System	Topic

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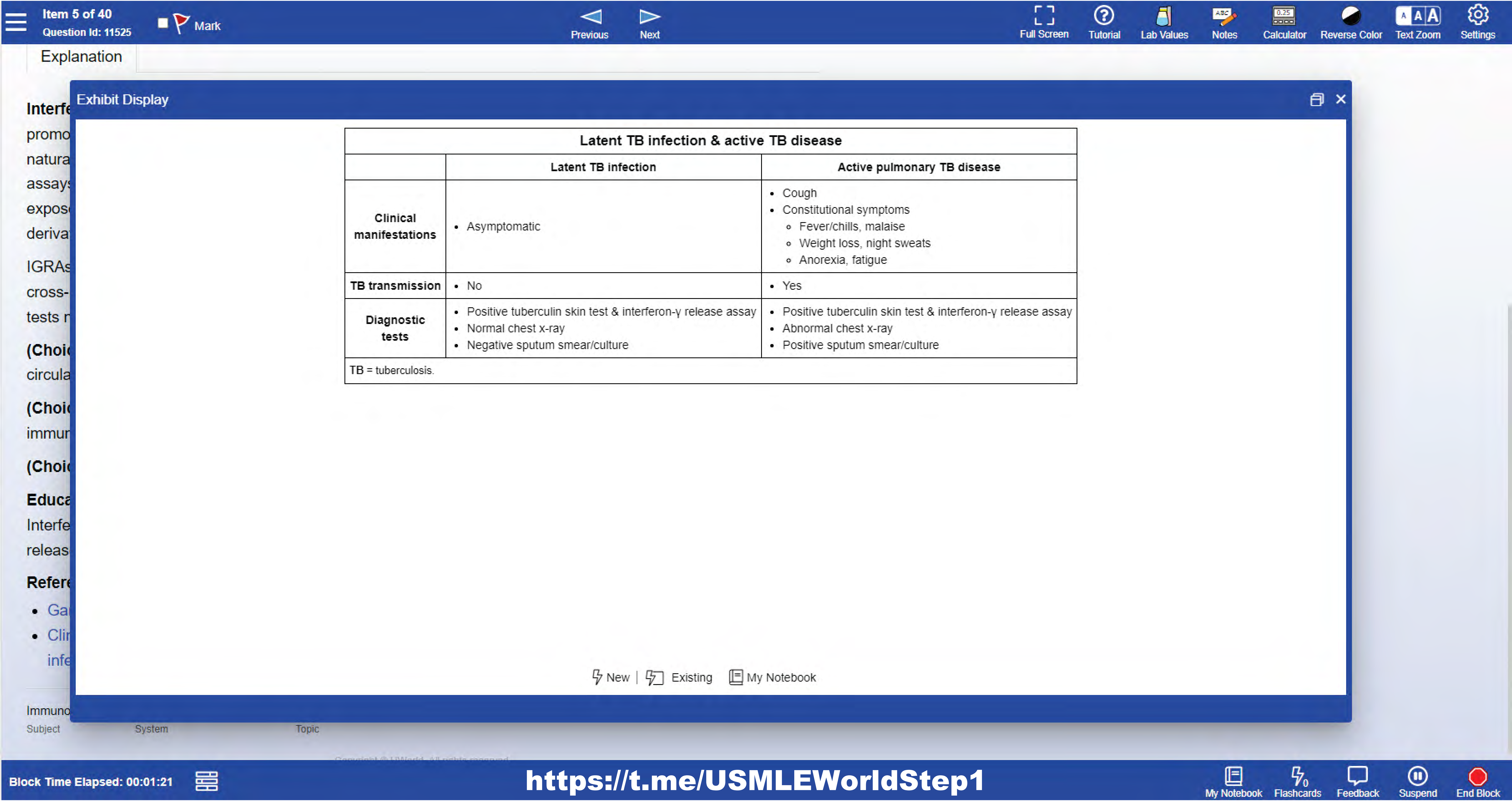

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Latent TB infection & active TB disease

	Latent TB infection	Active pulmonary TB disease
Clinical manifestations	• Asymptomatic	• Cough • Constitutional symptoms ∘ Fever/chills, malaise ∘ Weight loss, night sweats ∘ Anorexia, fatigue
TB transmission	• No	• Yes
Diagnostic tests	• Positive tuberculin skin test & interferon-γ release assay • Normal chest x-ray • Negative sputum smear/culture	• Positive tuberculin skin test & interferon-γ release assay • Abnormal chest x-ray • Positive sputum smear/culture

TB = tuberculosis.

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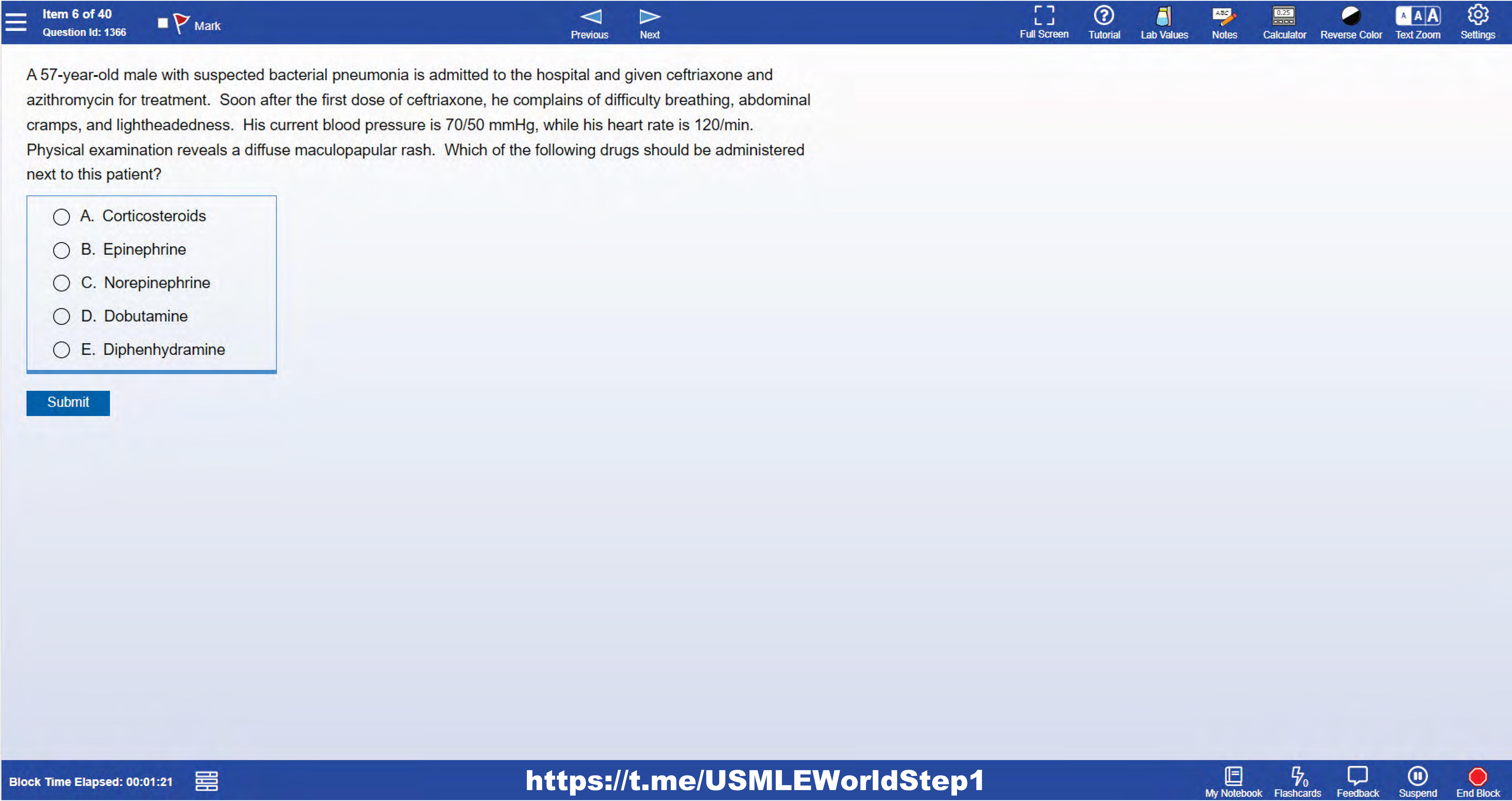
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A 57-year-old male with suspected bacterial pneumonia is admitted to the hospital and given ceftriaxone and azithromycin for treatment. Soon after the first dose of ceftriaxone, he complains of difficulty breathing, abdominal cramps, and lightheadedness. His current blood pressure is 70/50 mmHg, while his heart rate is 120/min. Physical examination reveals a diffuse maculopapular rash. Which of the following drugs should be administered next to this patient?

○ A. Corticosteroids
○ B. Epinephrine
○ C. Norepinephrine
○ D. Dobutamine
○ E. Diphenhydramine

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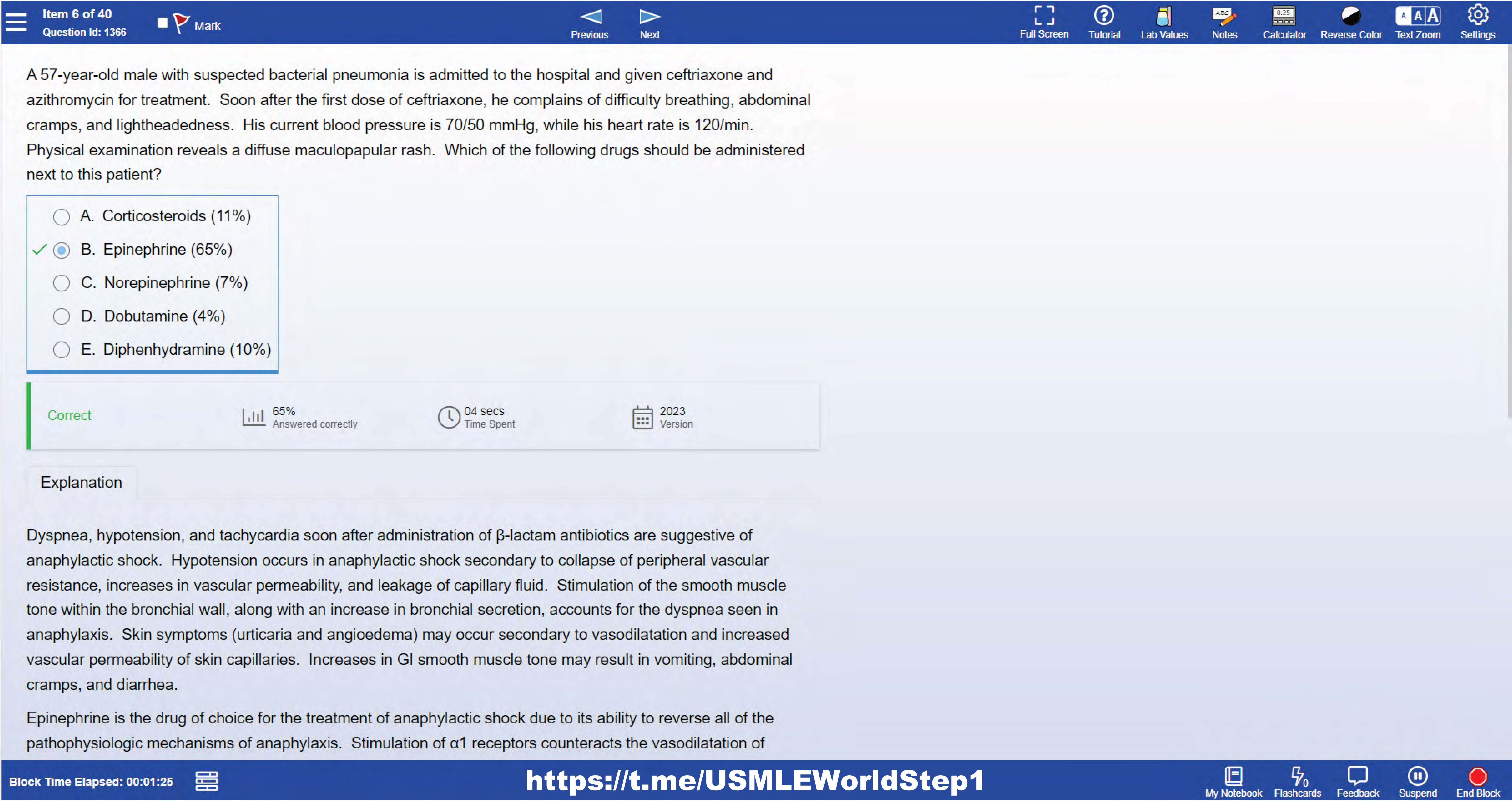
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○ A. Corticosteroids (11%)
✓ ● B. Epinephrine (65%)
○ C. Norepinephrine (7%)
○ D. Dobutamine (4%)
○ E. Diphenhydramine (10%)

Correct

65%
Answered correctly

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Explanation

Dyspnea, hypotension, and tachycardia soon after administration of β-lactam antibiotics are suggestive of anaphylactic shock. Hypotension occurs in anaphylactic shock secondary to collapse of peripheral vascular resistance, increases in vascular permeability, and leakage of capillary fluid. Stimulation of the smooth muscle tone within the bronchial wall, along with an increase in bronchial secretion, accounts for the dyspnea seen in anaphylaxis. Skin symptoms (urticaria and angioedema) may occur secondary to vasodilatation and increased vascular permeability of skin capillaries. Increases in GI smooth muscle tone may result in vomiting, abdominal cramps, and diarrhea.

Epinephrine is the drug of choice for the treatment of anaphylactic shock due to its ability to reverse all of the pathophysiologic mechanisms of anaphylaxis. Stimulation of α1 receptors counteracts the vasodilatation of

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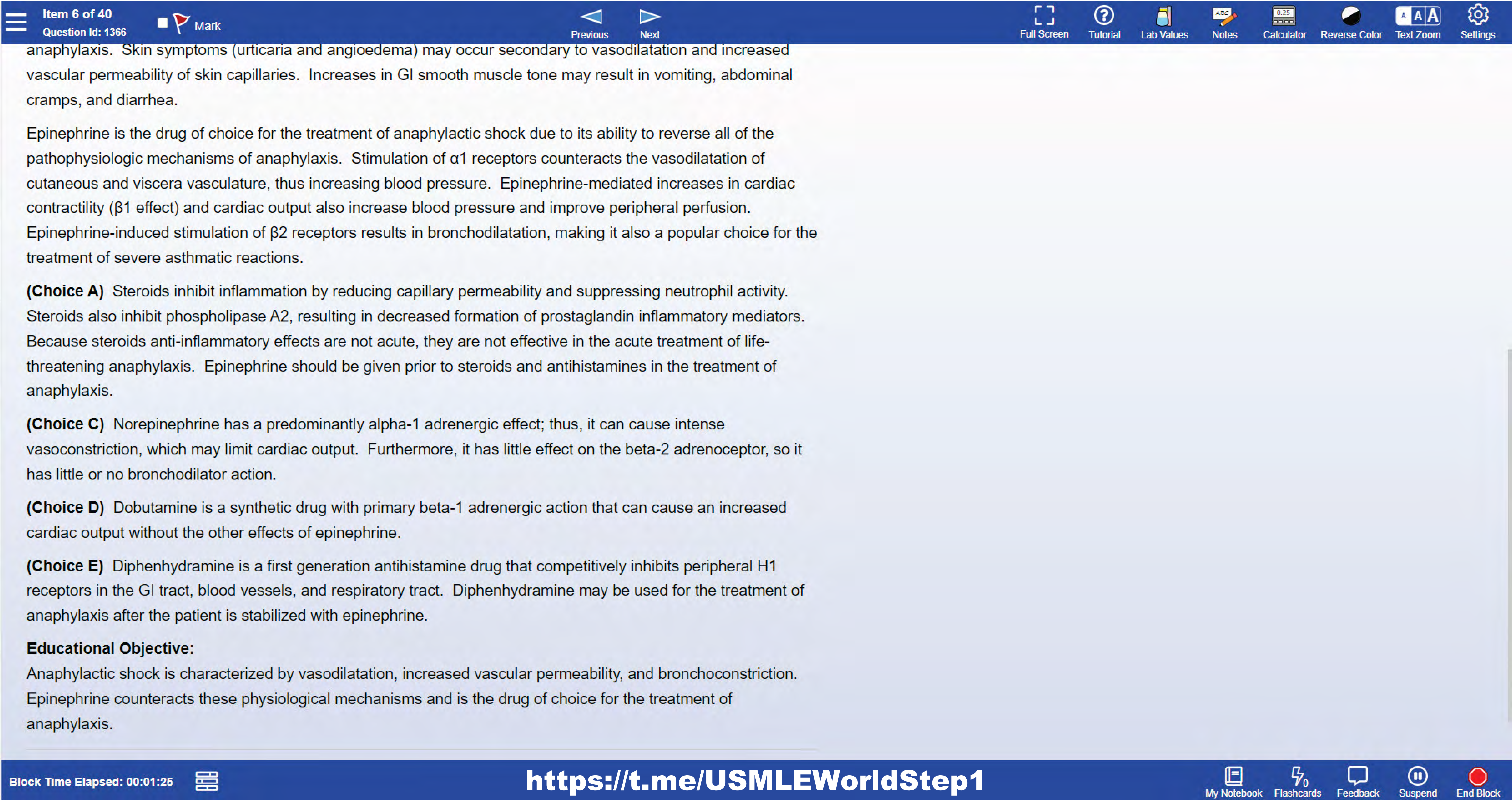
Epinephrine is the drug of choice for the treatment of anaphylactic shock due to its ability to reverse all of the pathophysiologic mechanisms of anaphylaxis. Stimulation of α1 receptors counteracts the vasodilatation of cutaneous and viscera vasculature, thus increasing blood pressure. Epinephrine-mediated increases in cardiac contractility (β1 effect) and cardiac output also increase blood pressure and improve peripheral perfusion. Epinephrine-induced stimulation of β2 receptors results in bronchodilatation, making it also a popular choice for the treatment of severe asthmatic reactions.

(Choice A) Steroids inhibit inflammation by reducing capillary permeability and suppressing neutrophil activity. Steroids also inhibit phospholipase A2, resulting in decreased formation of prostaglandin inflammatory mediators. Because steroids anti-inflammatory effects are not acute, they are not effective in the acute treatment of life-threatening anaphylaxis. Epinephrine should be given prior to steroids and antihistamines in the treatment of anaphylaxis.

(Choice C) Norepinephrine has a predominantly alpha-1 adrenergic effect; thus, it can cause intense vasoconstriction, which may limit cardiac output. Furthermore, it has little effect on the beta-2 adrenoceptor, so it has little or no bronchodilator action.

(Choice D) Dobutamine is a synthetic drug with primary beta-1 adrenergic action that can cause an increased cardiac output without the other effects of epinephrine.

(Choice E) Diphenhydramine is a first generation antihistamine drug that competitively inhibits peripheral H1 receptors in the GI tract, blood vessels, and respiratory tract. Diphenhydramine may be used for the treatment of



anaphylaxis. Skin symptoms (urticaria and angioedema) may occur secondary to vasodilatation and increased vascular permeability of skin capillaries. Increases in GI smooth muscle tone may result in vomiting, abdominal cramps, and diarrhea.

Epinephrine is the drug of choice for the treatment of anaphylactic shock due to its ability to reverse all of the pathophysiologic mechanisms of anaphylaxis. Stimulation of α1 receptors counteracts the vasodilatation of cutaneous and viscera vasculature, thus increasing blood pressure. Epinephrine-mediated increases in cardiac contractility (β1 effect) and cardiac output also increase blood pressure and improve peripheral perfusion. Epinephrine-induced stimulation of β2 receptors results in bronchodilatation, making it also a popular choice for the treatment of severe asthmatic reactions.

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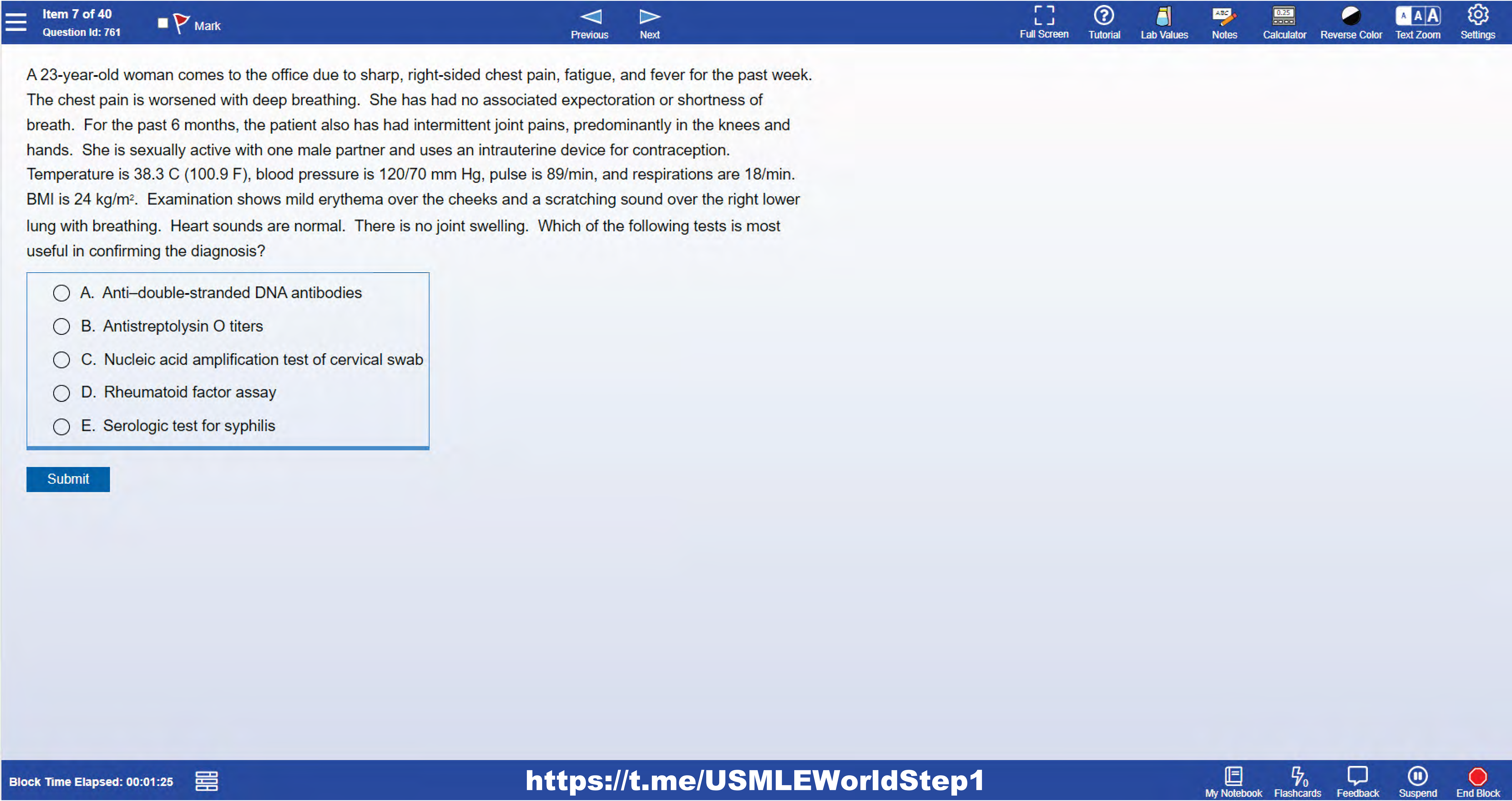
(Choice D) Dobutamine is a synthetic drug with primary beta-1 adrenergic action that can cause an increased cardiac output without the other effects of epinephrine.

(Choice E) Diphenhydramine is a first generation antihistamine drug that competitively inhibits peripheral H1 receptors in the GI tract, blood vessels, and respiratory tract. Diphenhydramine may be used for the treatment of anaphylaxis after the patient is stabilized with epinephrine.

Educational Objective:

Anaphylactic shock is characterized by vasodilatation, increased vascular permeability, and bronchoconstriction. Epinephrine counteracts these physiological mechanisms and is the drug of choice for the treatment of anaphylaxis.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A 23-year-old woman comes to the office due to sharp, right-sided chest pain, fatigue, and fever for the past week. The chest pain is worsened with deep breathing. She has had no associated expectoration or shortness of breath. For the past 6 months, the patient also has had intermittent joint pains, predominantly in the knees and hands. She is sexually active with one male partner and uses an intrauterine device for contraception. Temperature is 38.3 C (100.9 F), blood pressure is 120/70 mm Hg, pulse is 89/min, and respirations are 18/min. BMI is 24 kg/m^2. Examination shows mild erythema over the cheeks and a scratching sound over the right lower lung with breathing. Heart sounds are normal. There is no joint swelling. Which of the following tests is most useful in confirming the diagnosis?

○ A. Anti–double-stranded DNA antibodies
○ B. Antistreptolysin O titers
○ C. Nucleic acid amplification test of cervical swab
○ D. Rheumatoid factor assay
○ E. Serologic test for syphilis

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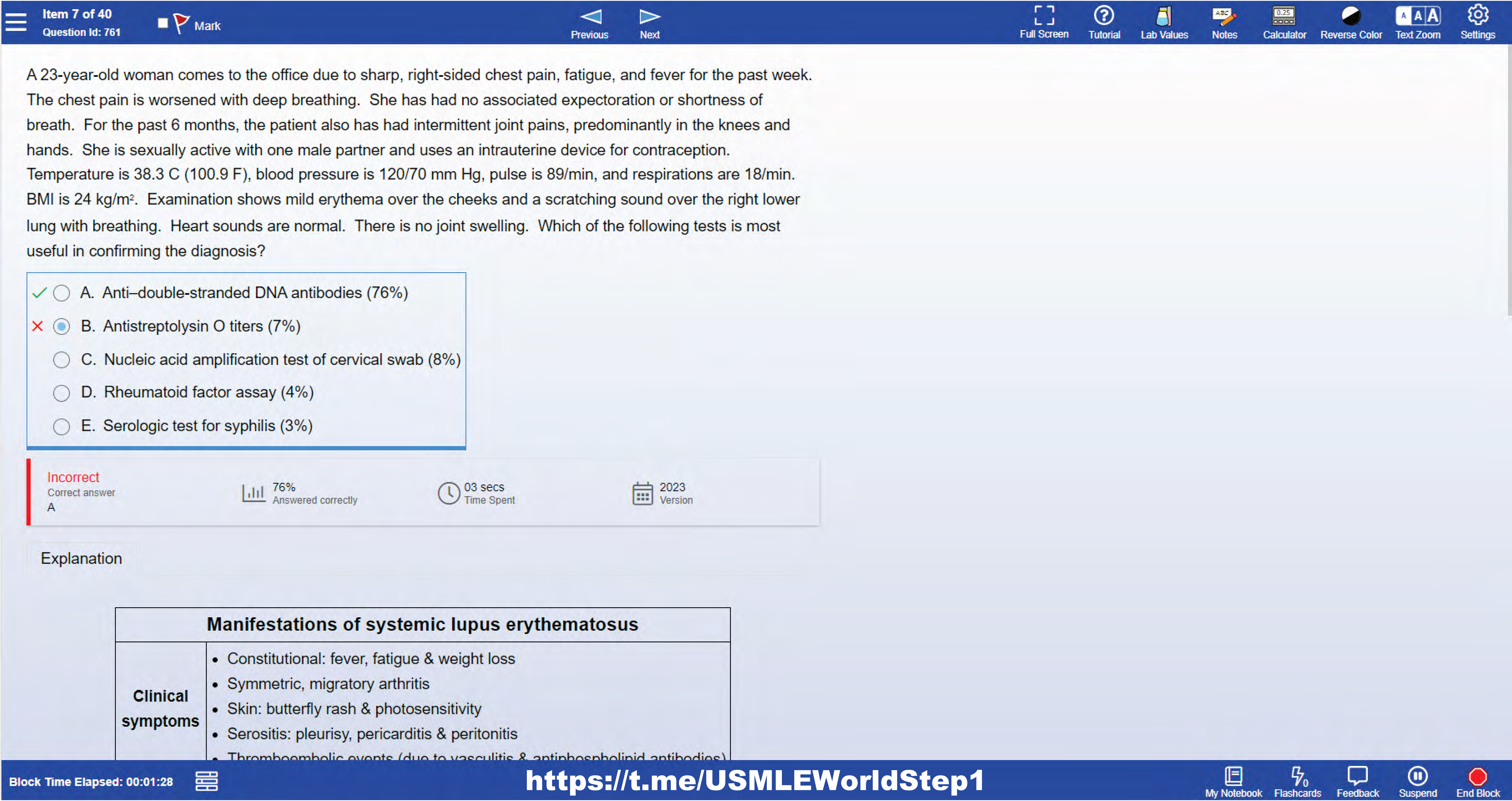
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✓ ○ A. Anti–double-stranded DNA antibodies (76%)
✗ ● B. Antistreptolysin O titers (7%)
○ C. Nucleic acid amplification test of cervical swab (8%)
○ D. Rheumatoid factor assay (4%)
○ E. Serologic test for syphilis (3%)

Incorrect
Correct answer
A

76%
Answered correctly

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Explanation

Manifestations of systemic lupus erythematosus	
Clinical symptoms	• Constitutional: fever, fatigue & weight loss • Symmetric, migratory arthritis • Skin: butterfly rash & photosensitivity • Serositis: pleurisy, pericarditis & peritonitis • Thromboembolic events (due to vasculitis & antiphospholipid antibodies)

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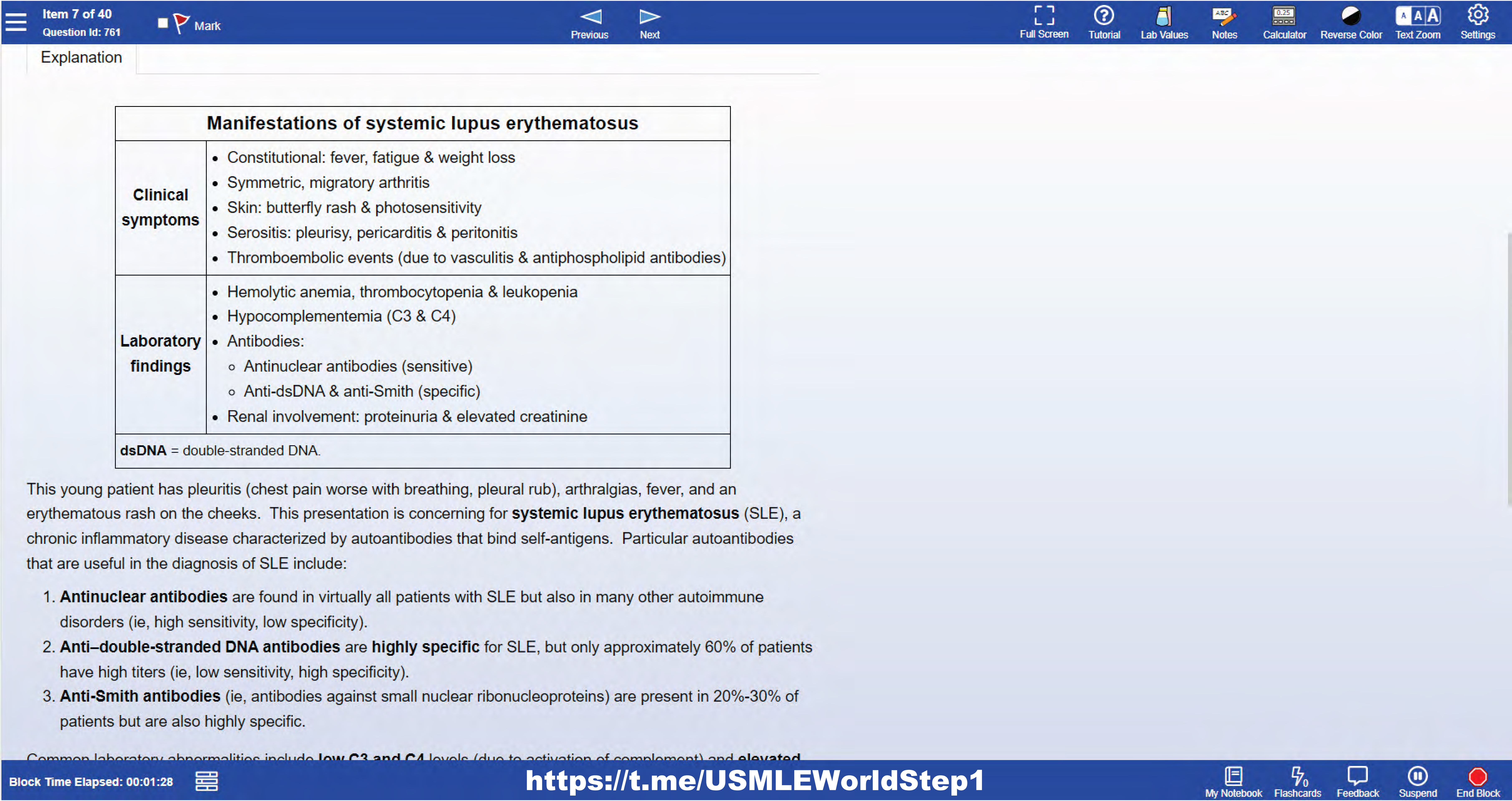
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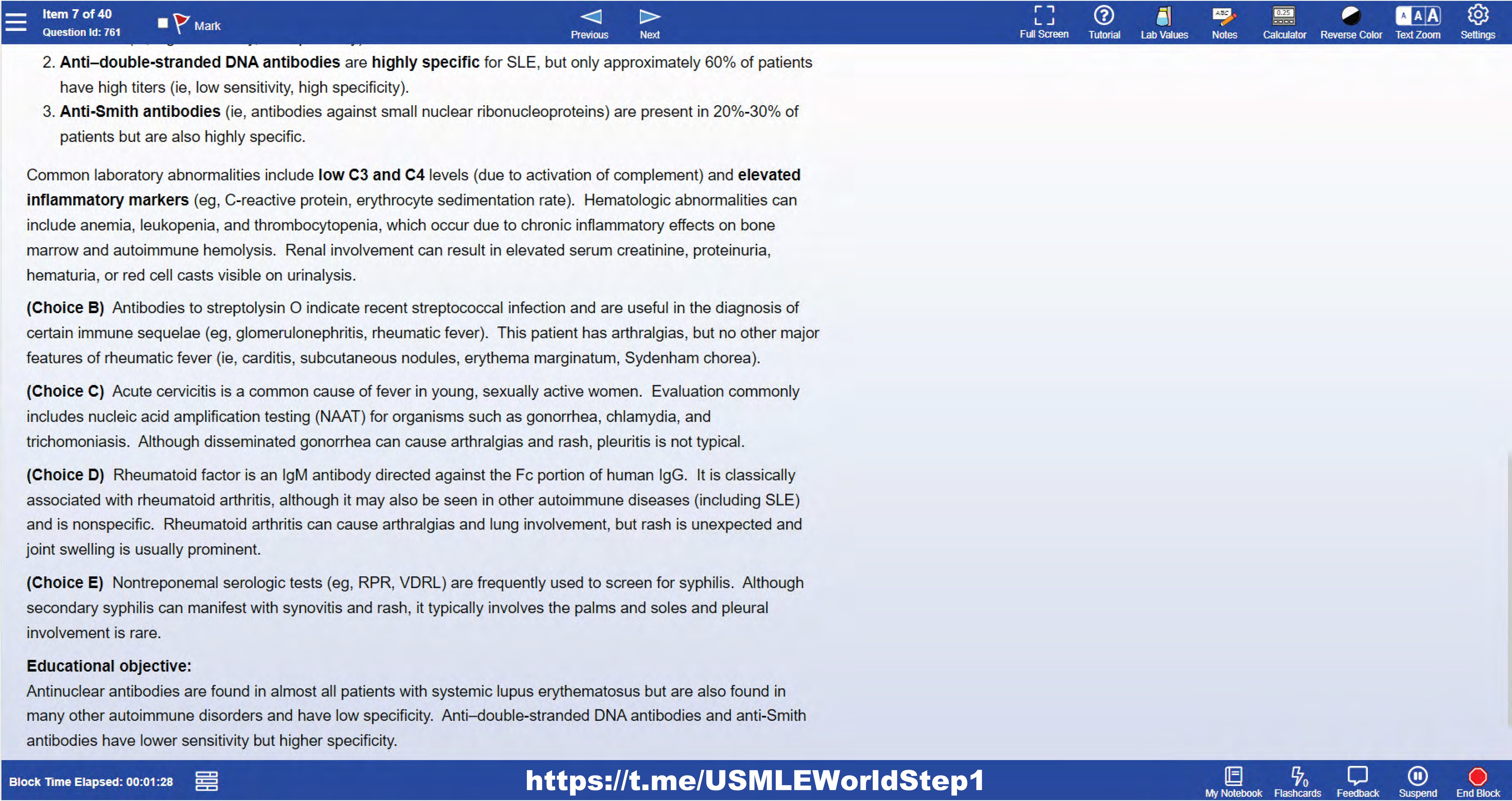
Manifestations of systemic lupus erythematosus	
Clinical symptoms	• Constitutional: fever, fatigue & weight loss • Symmetric, migratory arthritis • Skin: butterfly rash & photosensitivity • Serositis: pleurisy, pericarditis & peritonitis • Thromboembolic events (due to vasculitis & antiphospholipid antibodies)
Laboratory findings	• Hemolytic anemia, thrombocytopenia & leukopenia • Hypocomplementemia (C3 & C4) • Antibodies: ○ Antinuclear antibodies (sensitive) ○ Anti-dsDNA & anti-Smith (specific) • Renal involvement: proteinuria & elevated creatinine

dsDNA = double-stranded DNA.

This young patient has pleuritis (chest pain worse with breathing, pleural rub), arthralgias, fever, and an erythematous rash on the cheeks. This presentation is concerning for **systemic lupus erythematosus** (SLE), a chronic inflammatory disease characterized by autoantibodies that bind self-antigens. Particular autoantibodies that are useful in the diagnosis of SLE include:

1. **Antinuclear antibodies** are found in virtually all patients with SLE but also in many other autoimmune disorders (ie, high sensitivity, low specificity).
2. **Anti–double-stranded DNA antibodies** are **highly specific** for SLE, but only approximately 60% of patients have high titers (ie, low sensitivity, high specificity).
3. **Anti-Smith antibodies** (ie, antibodies against small nuclear ribonucleoproteins) are present in 20%-30% of patients but are also highly specific.

Common laboratory abnormalities include **low C3 and C4** levels (due to activation of complement) and **elevated**



2. **Anti–double-stranded DNA antibodies** are **highly specific** for SLE, but only approximately 60% of patients have high titers (ie, low sensitivity, high specificity).
3. **Anti-Smith antibodies** (ie, antibodies against small nuclear ribonucleoproteins) are present in 20%-30% of patients but are also highly specific.

Common laboratory abnormalities include **low C3 and C4** levels (due to activation of complement) and **elevated inflammatory markers** (eg, C-reactive protein, erythrocyte sedimentation rate). Hematologic abnormalities can include anemia, leukopenia, and thrombocytopenia, which occur due to chronic inflammatory effects on bone marrow and autoimmune hemolysis. Renal involvement can result in elevated serum creatinine, proteinuria, hematuria, or red cell casts visible on urinalysis.

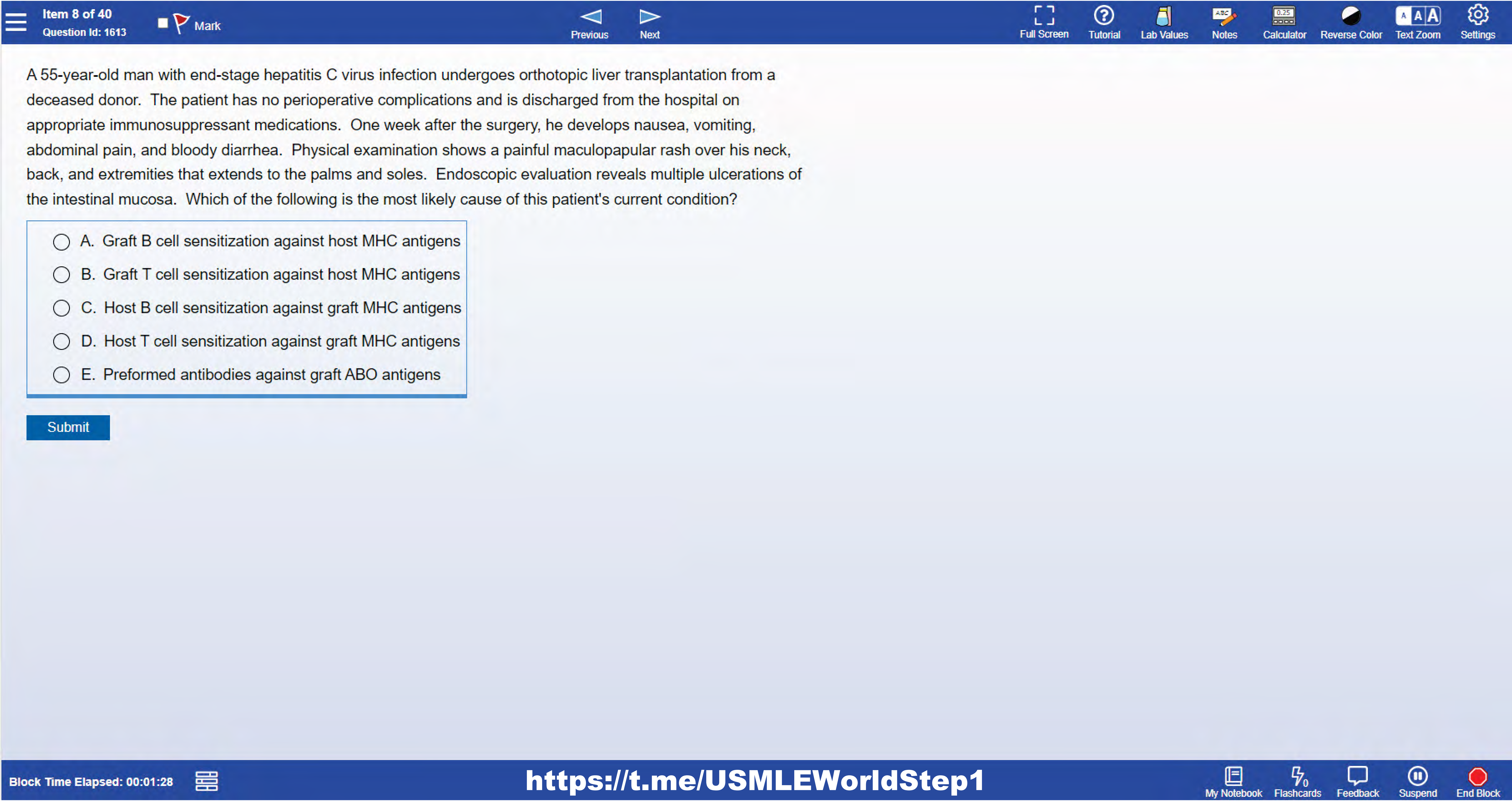
(Choice B) Antibodies to streptolysin O indicate recent streptococcal infection and are useful in the diagnosis of certain immune sequelae (eg, glomerulonephritis, rheumatic fever). This patient has arthralgias, but no other major features of rheumatic fever (ie, carditis, subcutaneous nodules, erythema marginatum, Sydenham chorea).

(Choice C) Acute cervicitis is a common cause of fever in young, sexually active women. Evaluation commonly includes nucleic acid amplification testing (NAAT) for organisms such as gonorrhea, chlamydia, and trichomoniasis. Although disseminated gonorrhea can cause arthralgias and rash, pleuritis is not typical.

(Choice D) Rheumatoid factor is an IgM antibody directed against the Fc portion of human IgG. It is classically associated with rheumatoid arthritis, although it may also be seen in other autoimmune diseases (including SLE) and is nonspecific. Rheumatoid arthritis can cause arthralgias and lung involvement, but rash is unexpected and joint swelling is usually prominent.

(Choice E) Nontreponemal serologic tests (eg, RPR, VDRL) are frequently used to screen for syphilis. Although secondary syphilis can manifest with synovitis and rash, it typically involves the palms and soles and pleural involvement is rare.

Educational objective:
Antinuclear antibodies are found in almost all patients with systemic lupus erythematosus but are also found in many other autoimmune disorders and have low specificity. Anti–double-stranded DNA antibodies and anti-Smith antibodies have lower sensitivity but higher specificity.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A 55-year-old man with end-stage hepatitis C virus infection undergoes orthotopic liver transplantation from a deceased donor. The patient has no perioperative complications and is discharged from the hospital on appropriate immunosuppressant medications. One week after the surgery, he develops nausea, vomiting, abdominal pain, and bloody diarrhea. Physical examination shows a painful maculopapular rash over his neck, back, and extremities that extends to the palms and soles. Endoscopic evaluation reveals multiple ulcerations of the intestinal mucosa. Which of the following is the most likely cause of this patient's current condition?

- ○ A. Graft B cell sensitization against host MHC antigens
- ○ B. Graft T cell sensitization against host MHC antigens
- ○ C. Host B cell sensitization against graft MHC antigens
- ○ D. Host T cell sensitization against graft MHC antigens
- ○ E. Preformed antibodies against graft ABO antigens

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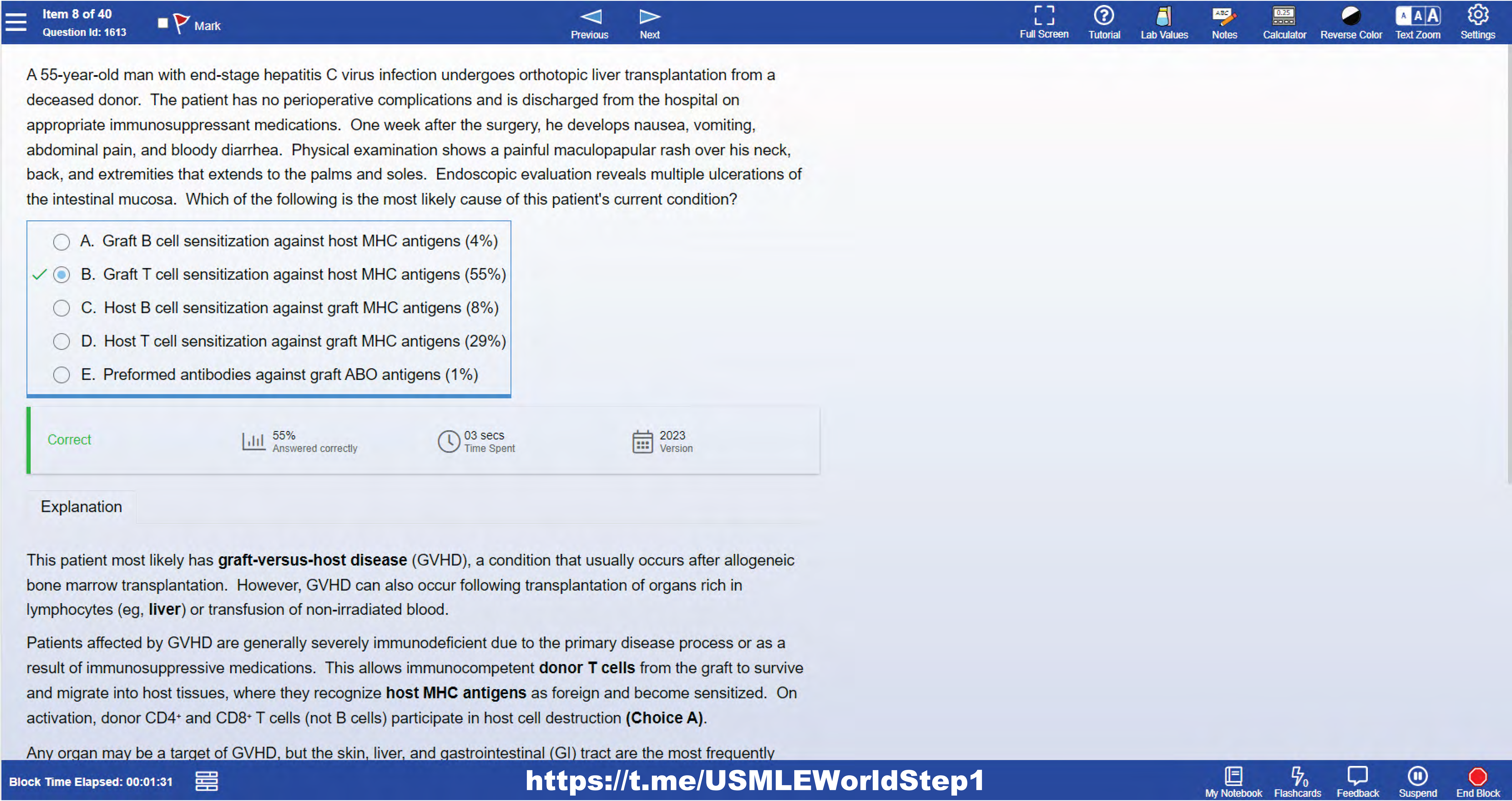

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○ A. Graft B cell sensitization against host MHC antigens (4%)

✓ ● B. Graft T cell sensitization against host MHC antigens (55%)

○ C. Host B cell sensitization against graft MHC antigens (8%)

○ D. Host T cell sensitization against graft MHC antigens (29%)

○ E. Preformed antibodies against graft ABO antigens (1%)

Correct

55%
Answered correctly

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Explanation

This patient most likely has **graft-versus-host disease** (GVHD), a condition that usually occurs after allogeneic bone marrow transplantation. However, GVHD can also occur following transplantation of organs rich in lymphocytes (eg, **liver**) or transfusion of non-irradiated blood.

Patients affected by GVHD are generally severely immunodeficient due to the primary disease process or as a result of immunosuppressive medications. This allows immunocompetent **donor T cells** from the graft to survive and migrate into host tissues, where they recognize **host MHC antigens** as foreign and become sensitized. On activation, donor $CD4^+$ and $CD8^+$ T cells (not B cells) participate in host cell destruction **(Choice A)**.

Any organ may be a target of GVHD, but the skin, liver, and gastrointestinal (GI) tract are the most frequently

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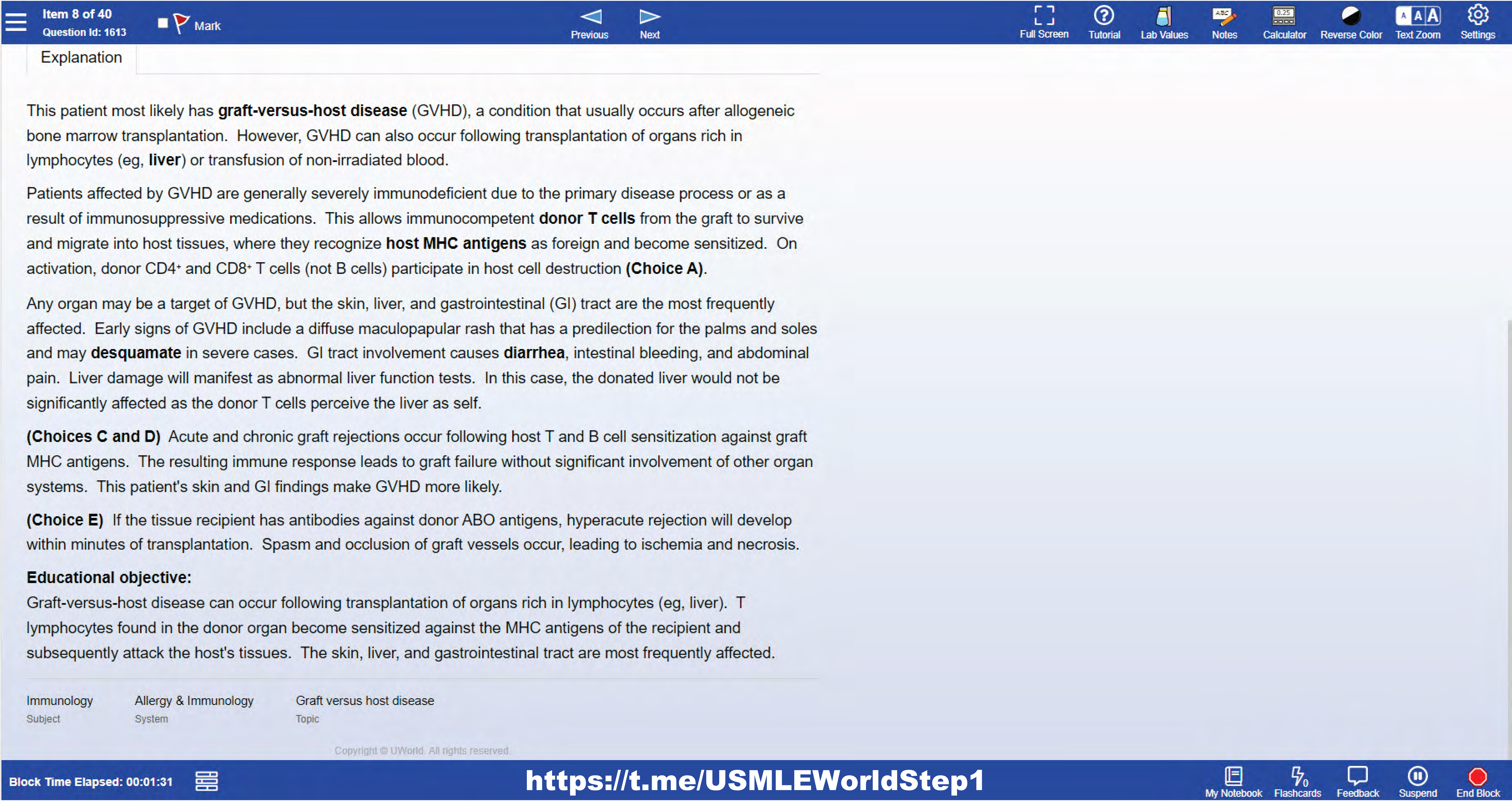

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Patients affected by GVHD are generally severely immunodeficient due to the primary disease process or as a result of immunosuppressive medications. This allows immunocompetent **donor T cells** from the graft to survive and migrate into host tissues, where they recognize **host MHC antigens** as foreign and become sensitized. On activation, donor $CD4^+$ and $CD8^+$ T cells (not B cells) participate in host cell destruction **(Choice A)**.

Any organ may be a target of GVHD, but the skin, liver, and gastrointestinal (GI) tract are the most frequently affected. Early signs of GVHD include a diffuse maculopapular rash that has a predilection for the palms and soles and may **desquamate** in severe cases. GI tract involvement causes **diarrhea**, intestinal bleeding, and abdominal pain. Liver damage will manifest as abnormal liver function tests. In this case, the donated liver would not be significantly affected as the donor T cells perceive the liver as self.

(Choices C and D) Acute and chronic graft rejections occur following host T and B cell sensitization against graft MHC antigens. The resulting immune response leads to graft failure without significant involvement of other organ systems. This patient's skin and GI findings make GVHD more likely.

(Choice E) If the tissue recipient has antibodies against donor ABO antigens, hyperacute rejection will develop within minutes of transplantation. Spasm and occlusion of graft vessels occur, leading to ischemia and necrosis.

Educational objective:
Graft-versus-host disease can occur following transplantation of organs rich in lymphocytes (eg, liver). T lymphocytes found in the donor organ become sensitized against the MHC antigens of the recipient and subsequently attack the host's tissues. The skin, liver, and gastrointestinal tract are most frequently affected.

Immunology	Allergy & Immunology	Graft versus host disease
Subject	System	Topic

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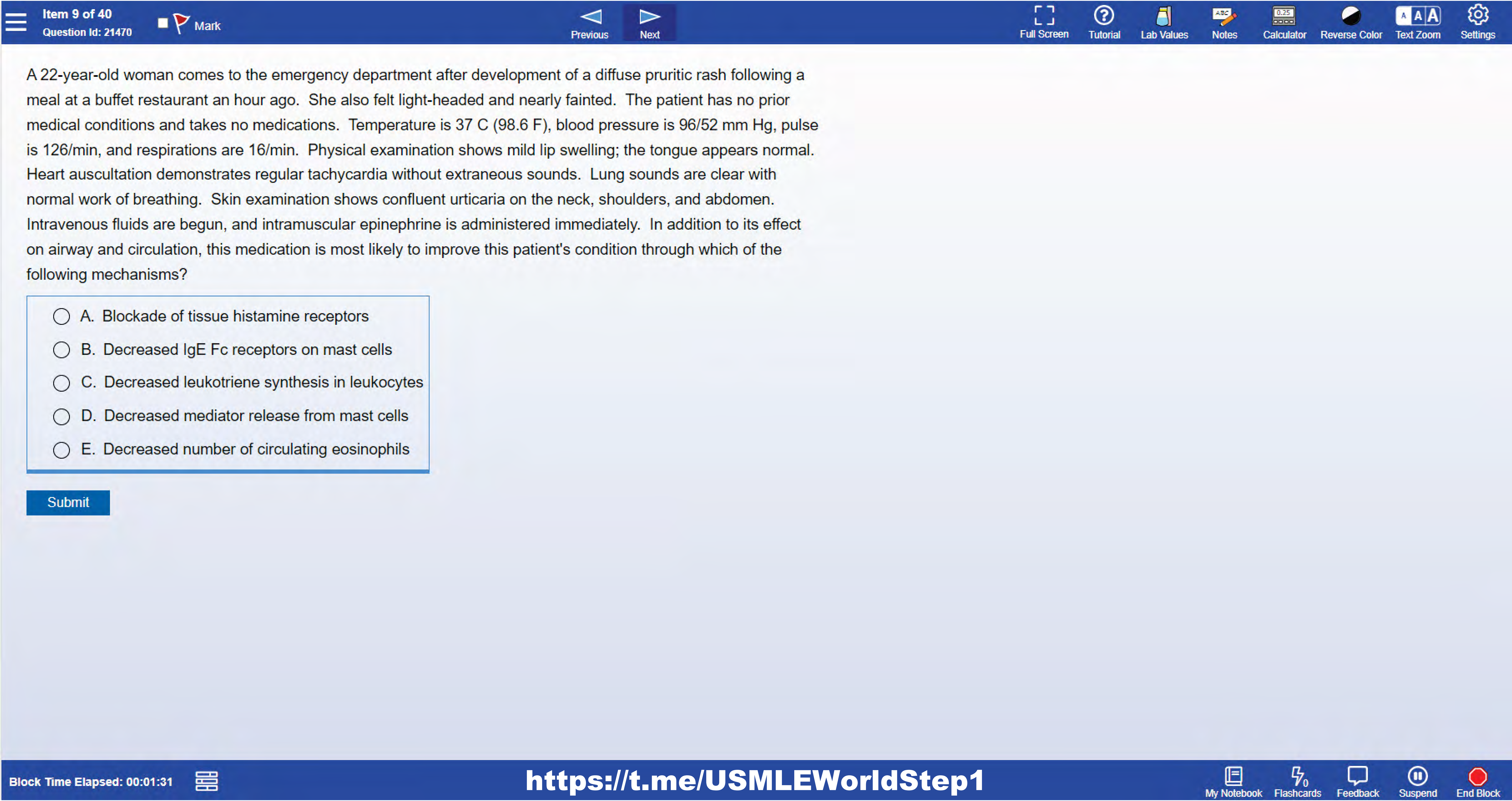
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Item 9 of 40
Question Id: 21470

A 22-year-old woman comes to the emergency department after development of a diffuse pruritic rash following a meal at a buffet restaurant an hour ago. She also felt light-headed and nearly fainted. The patient has no prior medical conditions and takes no medications. Temperature is 37 C (98.6 F), blood pressure is 96/52 mm Hg, pulse is 126/min, and respirations are 16/min. Physical examination shows mild lip swelling; the tongue appears normal. Heart auscultation demonstrates regular tachycardia without extraneous sounds. Lung sounds are clear with normal work of breathing. Skin examination shows confluent urticaria on the neck, shoulders, and abdomen. Intravenous fluids are begun, and intramuscular epinephrine is administered immediately. In addition to its effect on airway and circulation, this medication is most likely to improve this patient's condition through which of the following mechanisms?

○ A. Blockade of tissue histamine receptors
○ B. Decreased IgE Fc receptors on mast cells
○ C. Decreased leukotriene synthesis in leukocytes
○ D. Decreased mediator release from mast cells
○ E. Decreased number of circulating eosinophils

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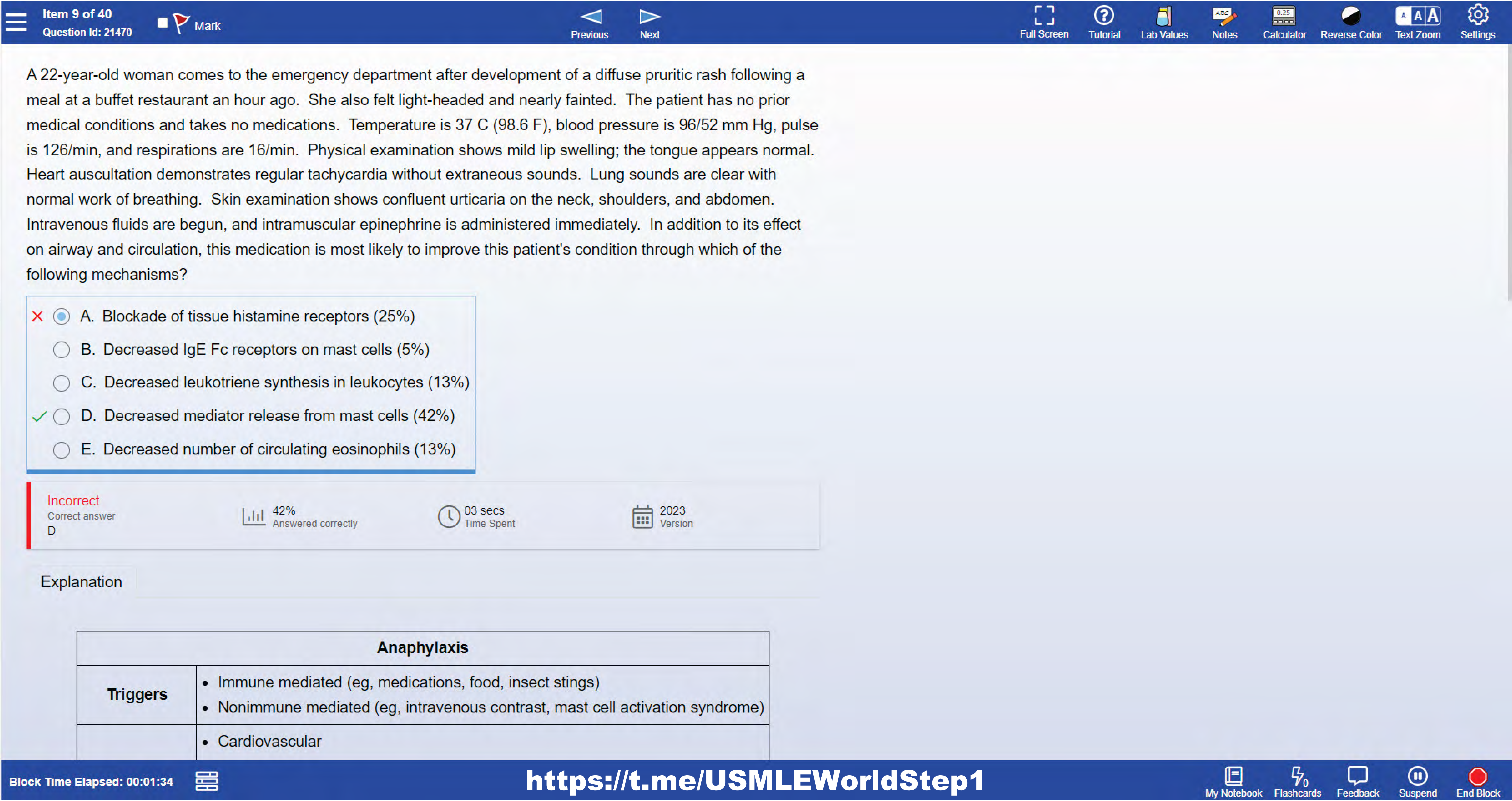
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✗ ● A. Blockade of tissue histamine receptors (25%)
○ B. Decreased IgE Fc receptors on mast cells (5%)
○ C. Decreased leukotriene synthesis in leukocytes (13%)
✓ ○ D. Decreased mediator release from mast cells (42%)
○ E. Decreased number of circulating eosinophils (13%)

Incorrect
Correct answer
D

42%
Answered correctly

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Explanation

Anaphylaxis	
Triggers	• Immune mediated (eg, medications, food, insect stings) • Nonimmune mediated (eg, intravenous contrast, mast cell activation syndrome)
	• Cardiovascular

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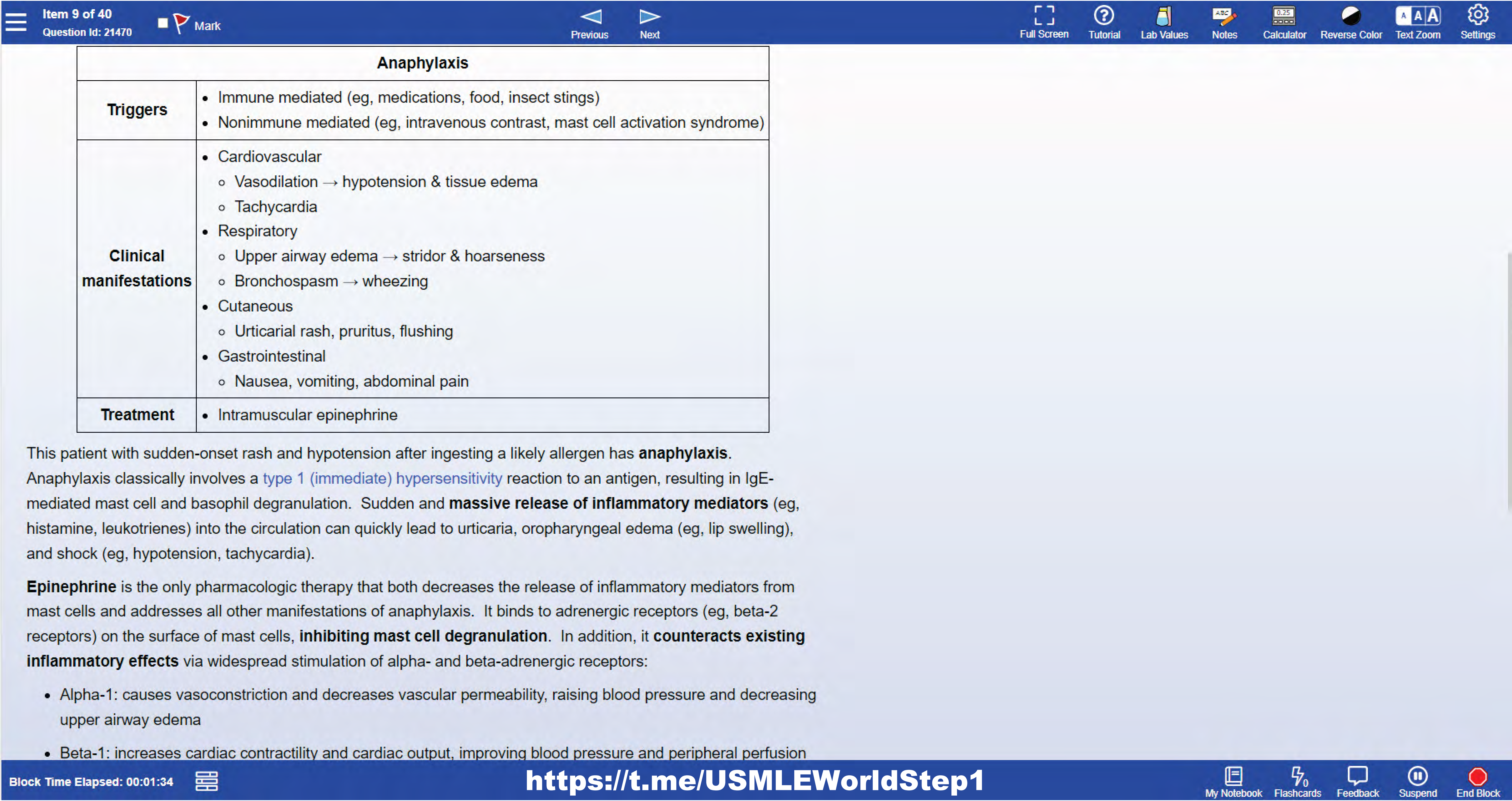
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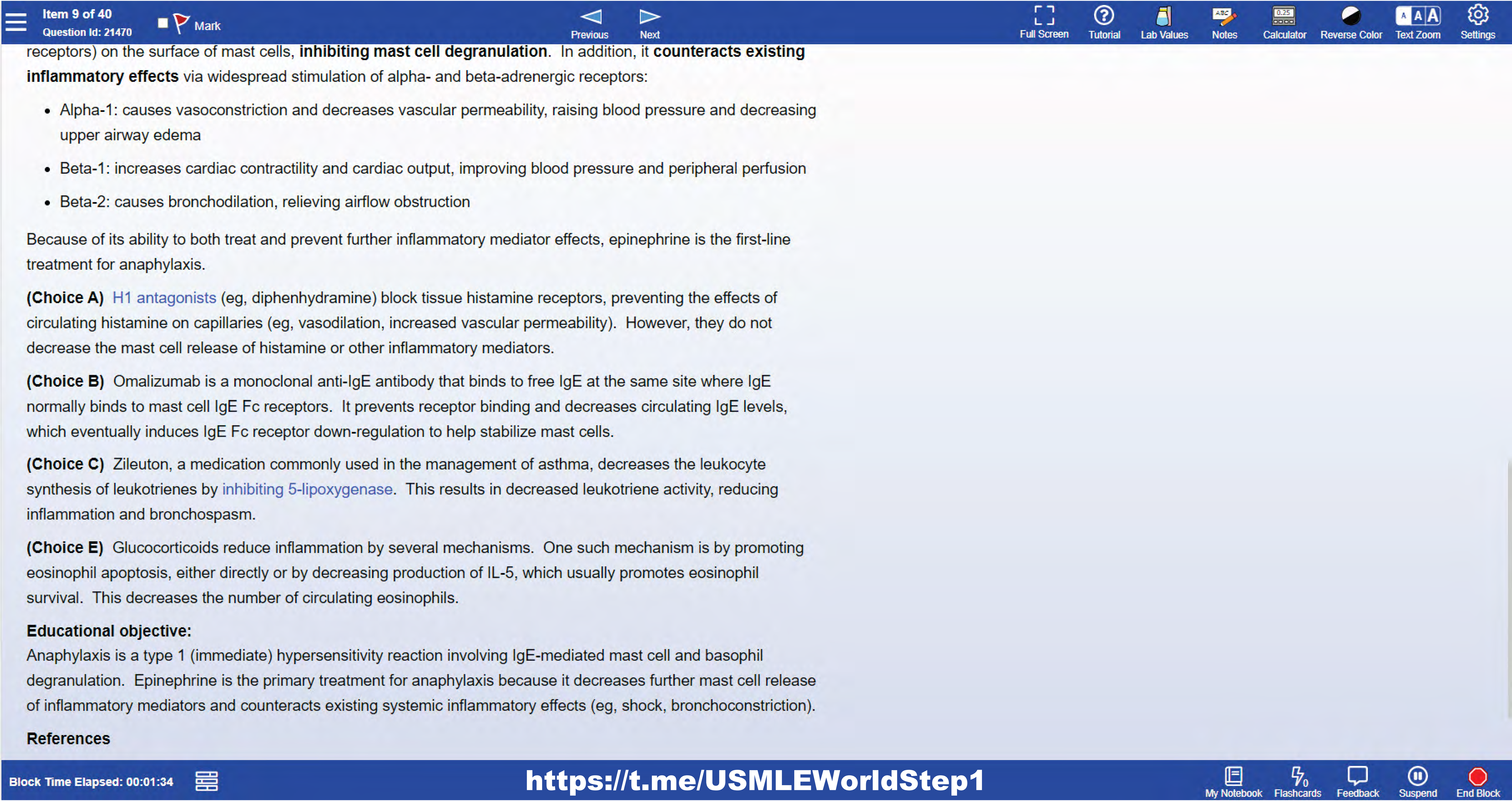
Anaphylaxis	
Triggers	• Immune mediated (eg, medications, food, insect stings) • Nonimmune mediated (eg, intravenous contrast, mast cell activation syndrome)
Clinical manifestations	• Cardiovascular ○ Vasodilation → hypotension & tissue edema ○ Tachycardia • Respiratory ○ Upper airway edema → stridor & hoarseness ○ Bronchospasm → wheezing • Cutaneous ○ Urticarial rash, pruritus, flushing • Gastrointestinal ○ Nausea, vomiting, abdominal pain
Treatment	• Intramuscular epinephrine

This patient with sudden-onset rash and hypotension after ingesting a likely allergen has **anaphylaxis**. Anaphylaxis classically involves a type 1 (immediate) hypersensitivity reaction to an antigen, resulting in IgE-mediated mast cell and basophil degranulation. Sudden and **massive release of inflammatory mediators** (eg, histamine, leukotrienes) into the circulation can quickly lead to urticaria, oropharyngeal edema (eg, lip swelling), and shock (eg, hypotension, tachycardia).

Epinephrine is the only pharmacologic therapy that both decreases the release of inflammatory mediators from mast cells and addresses all other manifestations of anaphylaxis. It binds to adrenergic receptors (eg, beta-2 receptors) on the surface of mast cells, **inhibiting mast cell degranulation**. In addition, it **counteracts existing inflammatory effects** via widespread stimulation of alpha- and beta-adrenergic receptors:

- Alpha-1: causes vasoconstriction and decreases vascular permeability, raising blood pressure and decreasing upper airway edema
- Beta-1: increases cardiac contractility and cardiac output, improving blood pressure and peripheral perfusion



receptors) on the surface of mast cells, **inhibiting mast cell degranulation**. In addition, it **counteracts existing inflammatory effects** via widespread stimulation of alpha- and beta-adrenergic receptors:

- Alpha-1: causes vasoconstriction and decreases vascular permeability, raising blood pressure and decreasing upper airway edema
- Beta-1: increases cardiac contractility and cardiac output, improving blood pressure and peripheral perfusion
- Beta-2: causes bronchodilation, relieving airflow obstruction

Because of its ability to both treat and prevent further inflammatory mediator effects, epinephrine is the first-line treatment for anaphylaxis.

(Choice A) H1 antagonists (eg, diphenhydramine) block tissue histamine receptors, preventing the effects of circulating histamine on capillaries (eg, vasodilation, increased vascular permeability). However, they do not decrease the mast cell release of histamine or other inflammatory mediators.

(Choice B) Omalizumab is a monoclonal anti-IgE antibody that binds to free IgE at the same site where IgE normally binds to mast cell IgE Fc receptors. It prevents receptor binding and decreases circulating IgE levels, which eventually induces IgE Fc receptor down-regulation to help stabilize mast cells.

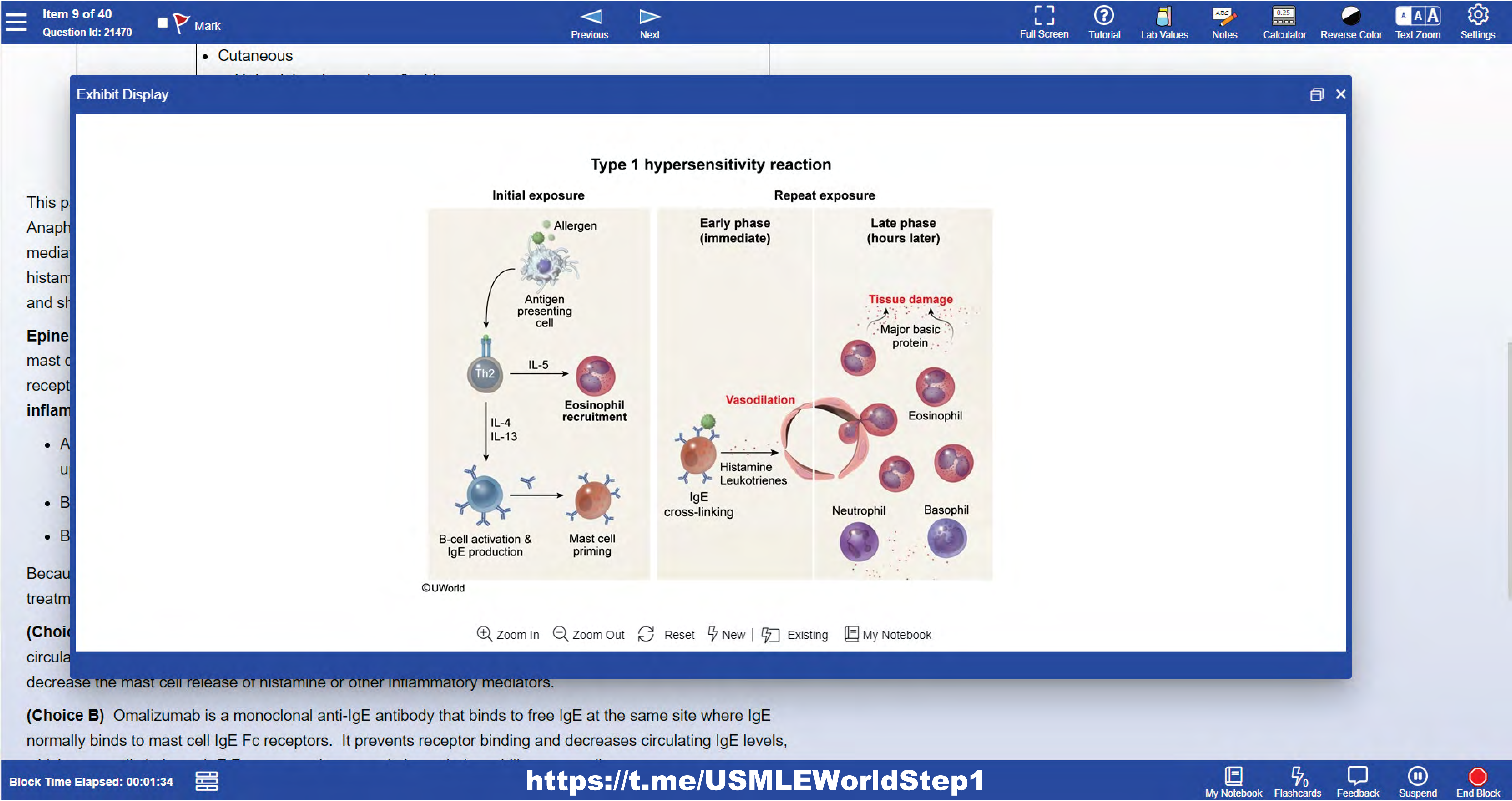
(Choice C) Zileuton, a medication commonly used in the management of asthma, decreases the leukocyte synthesis of leukotrienes by inhibiting 5-lipoxygenase. This results in decreased leukotriene activity, reducing inflammation and bronchospasm.

(Choice E) Glucocorticoids reduce inflammation by several mechanisms. One such mechanism is by promoting eosinophil apoptosis, either directly or by decreasing production of IL-5, which usually promotes eosinophil survival. This decreases the number of circulating eosinophils.

Educational objective:

Anaphylaxis is a type 1 (immediate) hypersensitivity reaction involving IgE-mediated mast cell and basophil degranulation. Epinephrine is the primary treatment for anaphylaxis because it decreases further mast cell release of inflammatory mediators and counteracts existing systemic inflammatory effects (eg, shock, bronchoconstriction).

References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decrease the mast cell release of histamine or other inflammatory mediators.

(Choice B) Omalizumab is a monoclonal anti-IgE antibody that binds to free IgE at the same site where IgE normally binds to mast cell IgE Fc receptors. It prevents receptor binding and decreases circulating IgE levels,

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Type 1 hypersensitivity reaction

Initial exposure
Repeat exposure
Early phase (immediate)
Late phase (hours later)
Allergen
Antigen presenting cell
Th2
IL-5
Eosinophil recruitment
IL-4
IL-13
B-cell activation & IgE production
Mast cell priming
Vasodilation
IgE cross-linking
Histamine
Leukotrienes
Tissue damage
Major basic protein
Eosinophil
Neutrophil
Basophil

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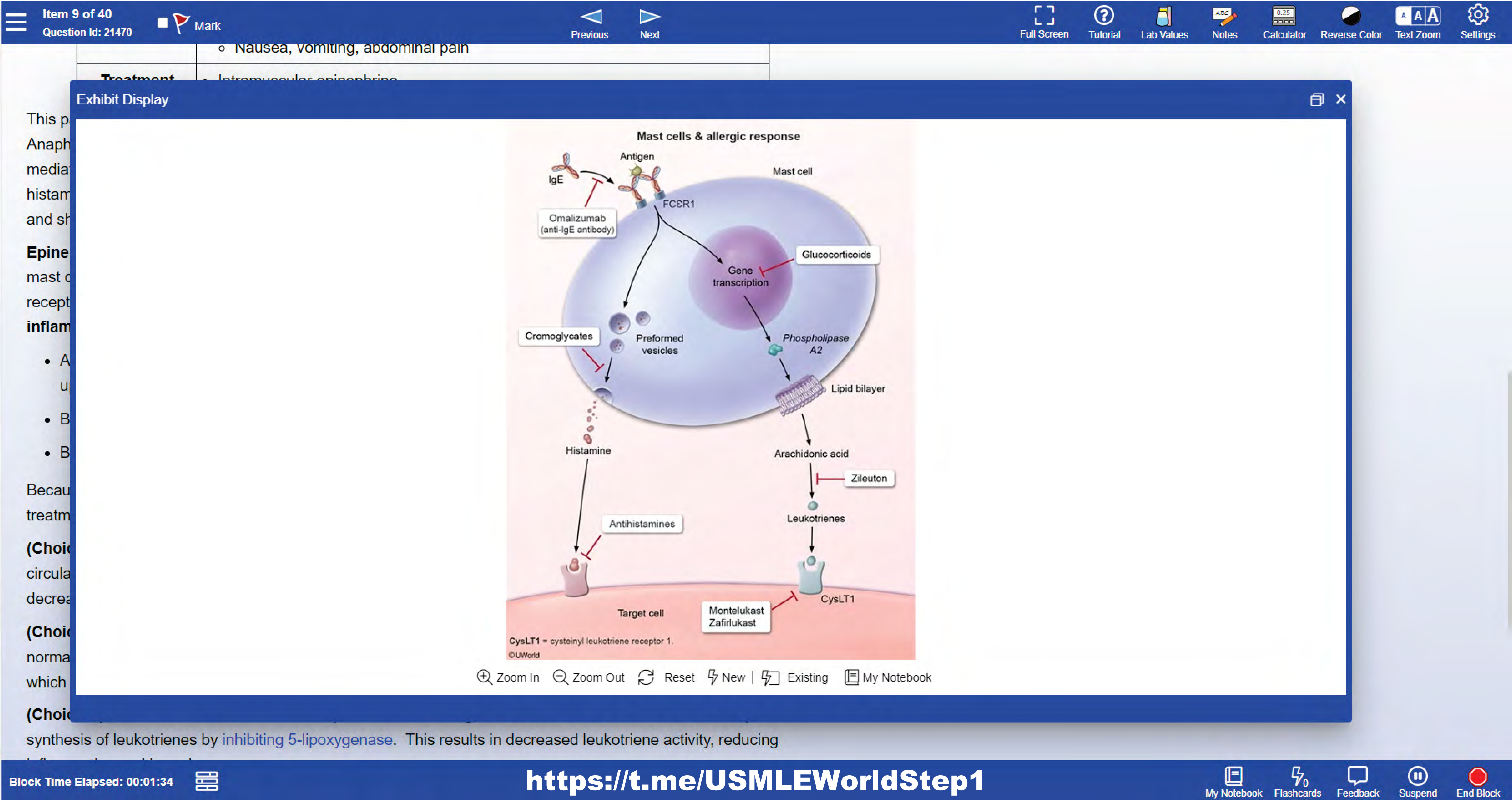
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Mast cells & allergic response
Antigen
IgE
Mast cell
FCεR1
Omalizumab
(anti-IgE antibody)
Glucocorticoids
Gene
transcription
Cromoglycates
Preformed
vesicles
Phospholipase
A2
Lipid bilayer
Histamine
Arachidonic acid
Zileuton
Leukotrienes
Antihistamines
CysLT1
Target cell
Montelukast
Zafirlukast
CysLT1 = cysteinyl leukotriene receptor 1.
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- Nausea, vomiting, abdominal pain

Treatment - Intramuscular epinephrine

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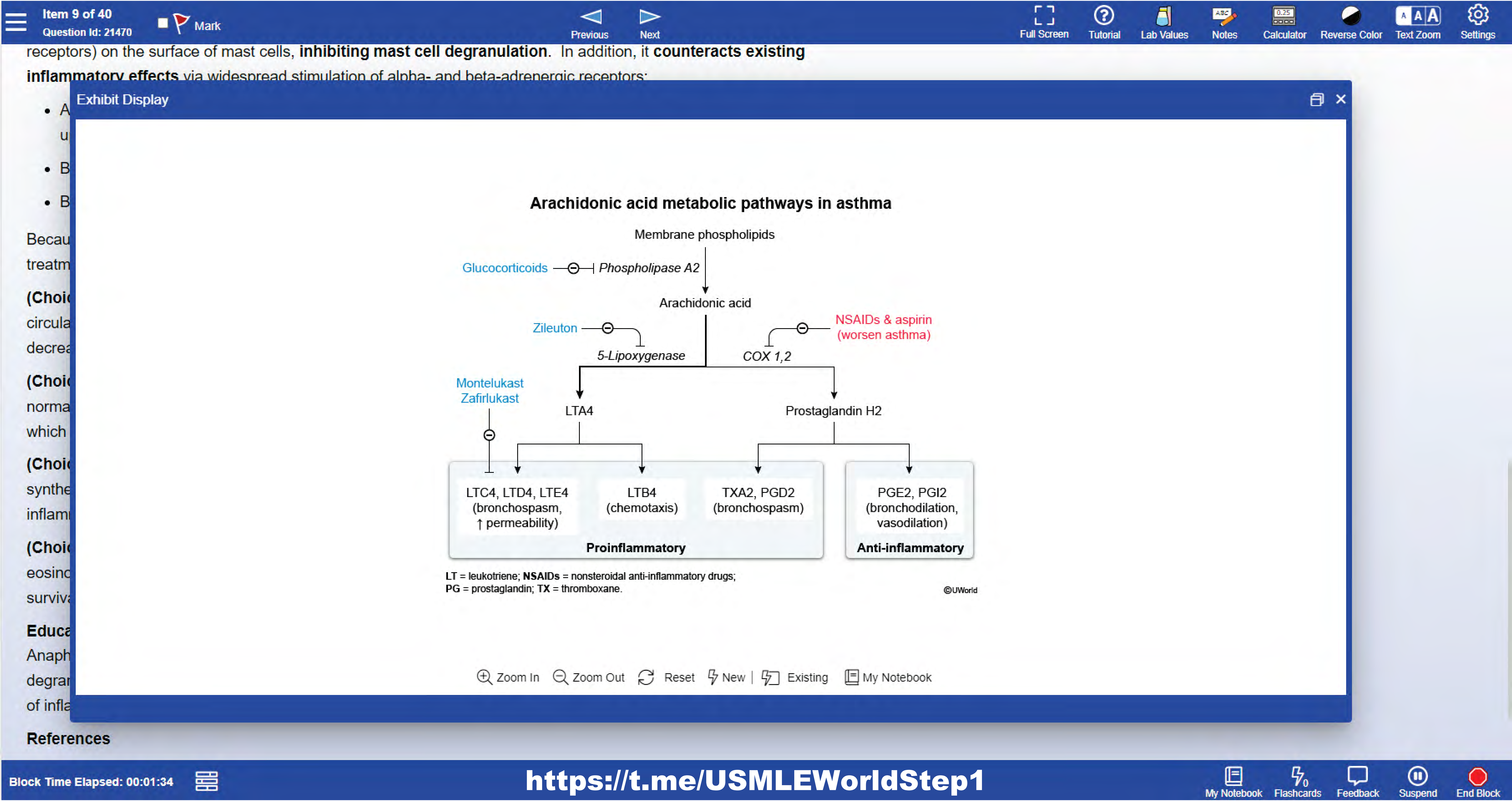
synthesis of leukotrienes by inhibiting 5-lipoxygenase. This results in decreased leukotriene activity, reducing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References

Arachidonic acid metabolic pathways in asthma

Membrane phospholipids
Glucocorticoids
Phospholipase A2
Arachidonic acid
Zileuton
5-Lipoxygenase
COX 1,2
NSAIDs & aspirin (worsen asthma)
Montelukast
Zafirlukast
LTA4
Prostaglandin H2
LTC4, LTD4, LTE4 (bronchospasm, ↑ permeability)
LTB4 (chemotaxis)
TXA2, PGD2 (bronchospasm)
PGE2, PGI2 (bronchodilation, vasodilation)
Proinflammatory
Anti-inflammatory

LT = leukotriene; **NSAIDs** = nonsteroidal anti-inflammatory drugs;
PG = prostaglandin; TX = thromboxane.

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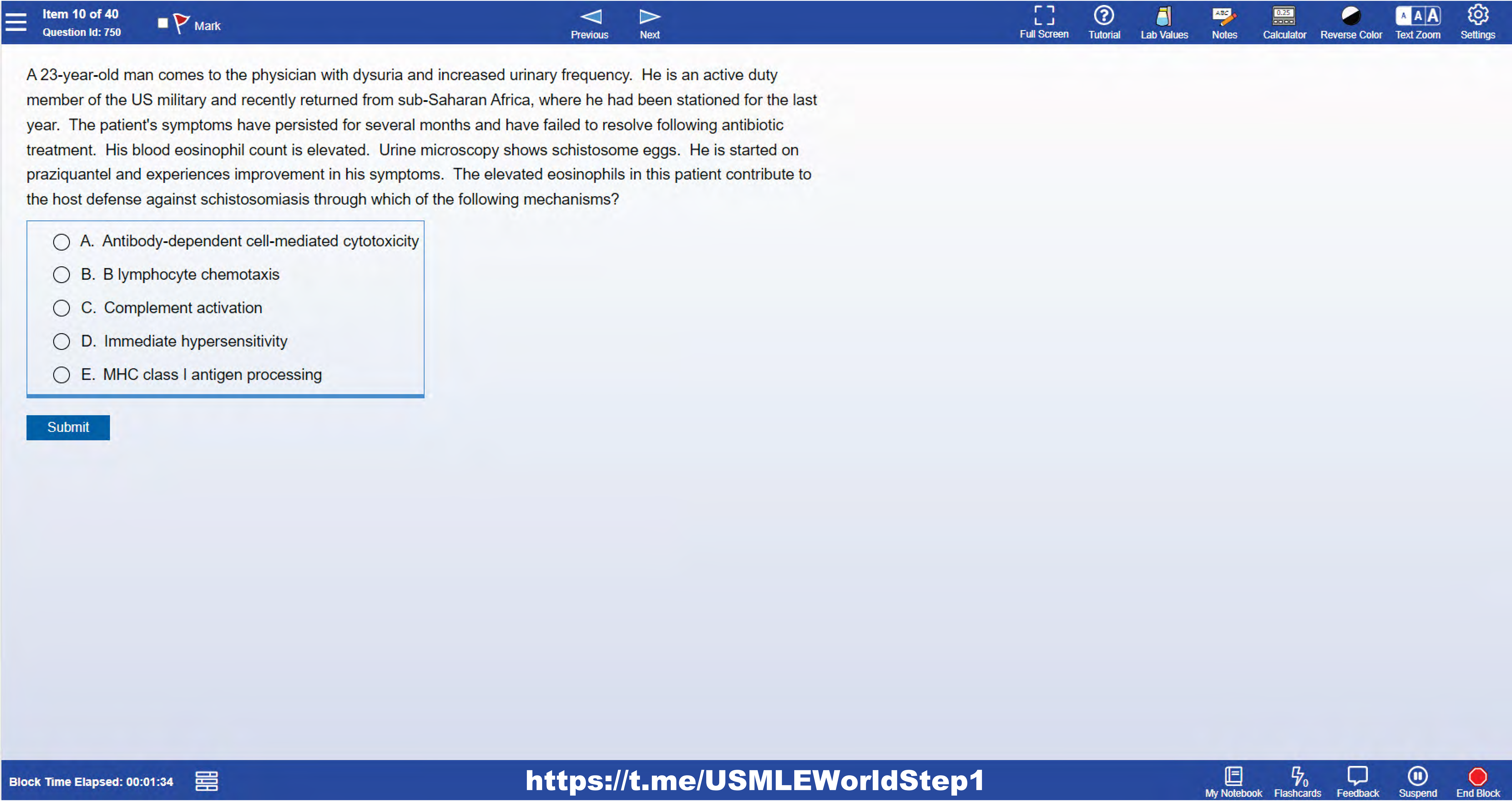
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Item 10 of 40
Question Id: 750

A 23-year-old man comes to the physician with dysuria and increased urinary frequency. He is an active duty member of the US military and recently returned from sub-Saharan Africa, where he had been stationed for the last year. The patient's symptoms have persisted for several months and have failed to resolve following antibiotic treatment. His blood eosinophil count is elevated. Urine microscopy shows schistosome eggs. He is started on praziquantel and experiences improvement in his symptoms. The elevated eosinophils in this patient contribute to the host defense against schistosomiasis through which of the following mechanisms?

○ A. Antibody-dependent cell-mediated cytotoxicity
○ B. B lymphocyte chemotaxis
○ C. Complement activation
○ D. Immediate hypersensitivity
○ E. MHC class I antigen processing

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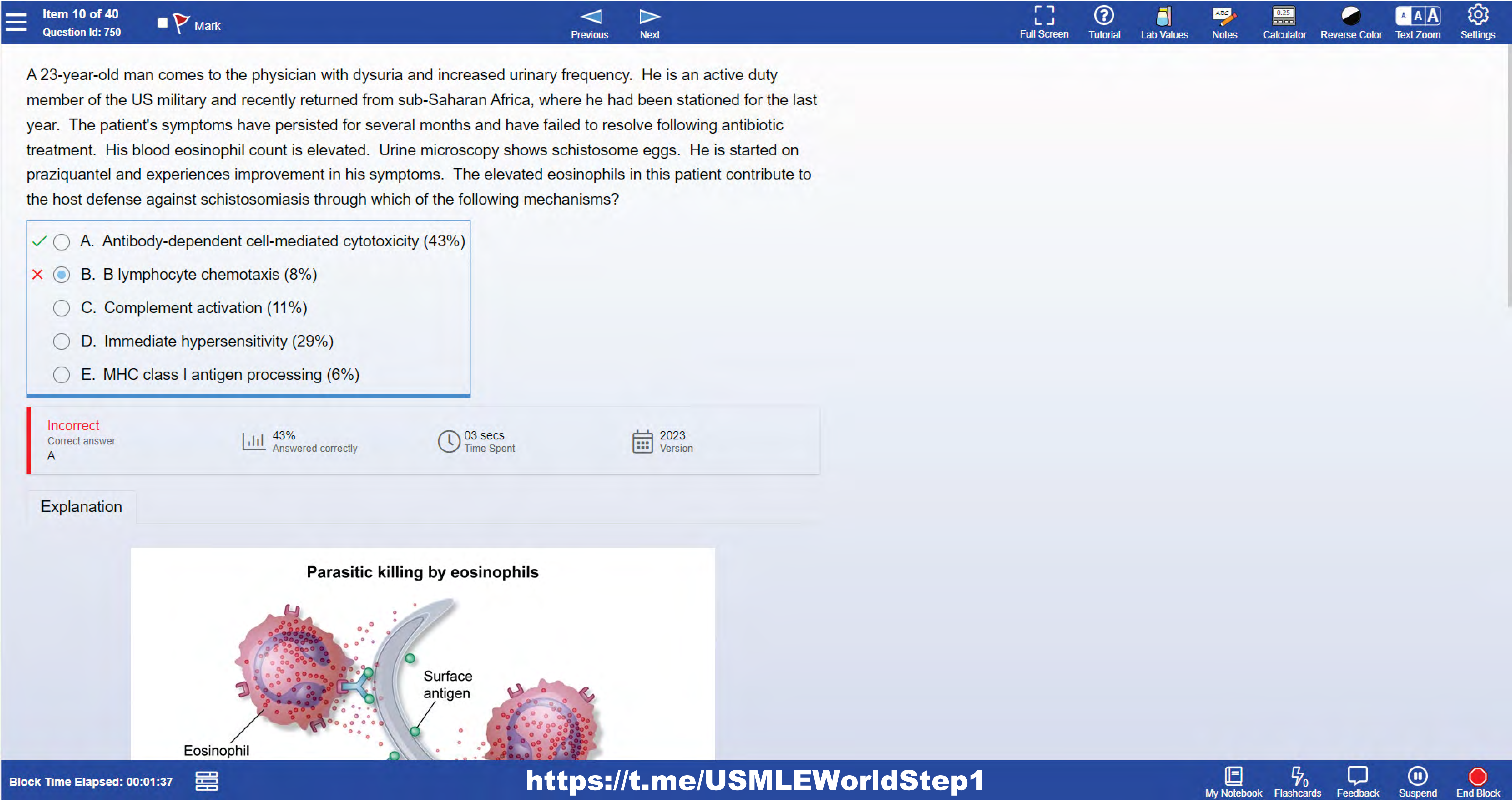
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- ✓ ○ A. Antibody-dependent cell-mediated cytotoxicity (43%)
- ✗ ● B. B lymphocyte chemotaxis (8%)
- ○ C. Complement activation (11%)
- ○ D. Immediate hypersensitivity (29%)
- ○ E. MHC class I antigen processing (6%)

Incorrect
Correct answer
A

43%
Answered correctly

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Explanation

Parasitic killing by eosinophils

Surface antigen
Eosinophil

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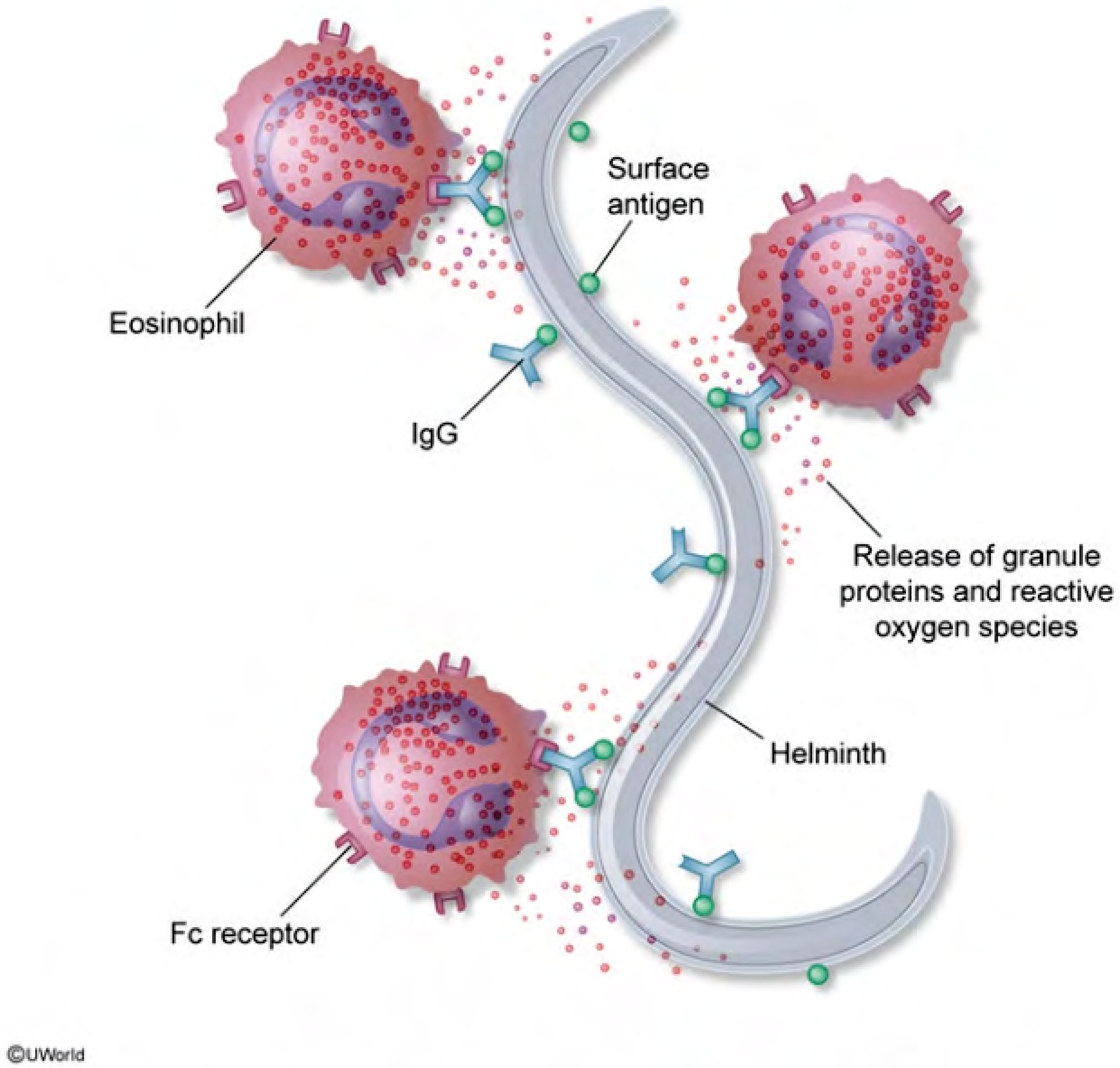
Parasitic killing by eosinophils


Eosinophil
Surface antigen
IgG
Release of granule proteins and reactive oxygen species
Helminth
Fc receptor

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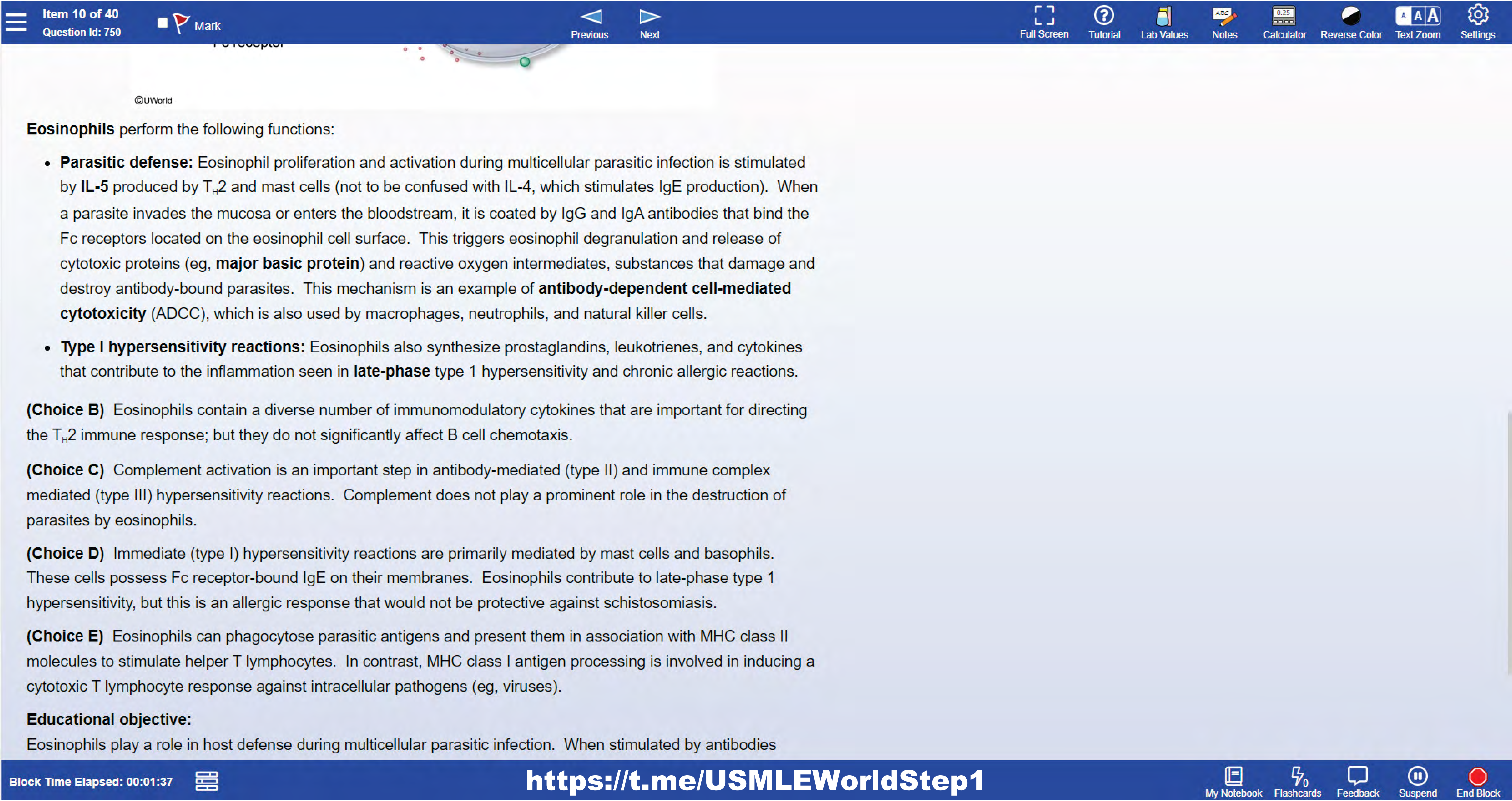

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Eosinophils perform the following functions:

- **Parasitic defense:** Eosinophil proliferation and activation during multicellular parasitic infection is stimulated by **IL-5** produced by T$_H$2 and mast cells (not to be confused with IL-4, which stimulates IgE production). When a parasite invades the mucosa or enters the bloodstream, it is coated by IgG and IgA antibodies that bind the Fc receptors located on the eosinophil cell surface. This triggers eosinophil degranulation and release of cytotoxic proteins (eg, **major basic protein**) and reactive oxygen intermediates, substances that damage and destroy antibody-bound parasites. This mechanism is an example of **antibody-dependent cell-mediated cytotoxicity** (ADCC), which is also used by macrophages, neutrophils, and natural killer cells.
- **Type I hypersensitivity reactions:** Eosinophils also synthesize prostaglandins, leukotrienes, and cytokines that contribute to the inflammation seen in **late-phase** type 1 hypersensitivity and chronic allergic reactions.

(Choice B) Eosinophils contain a diverse number of immunomodulatory cytokines that are important for directing the T$_H$2 immune response; but they do not significantly affect B cell chemotaxis.

(Choice C) Complement activation is an important step in antibody-mediated (type II) and immune complex mediated (type III) hypersensitivity reactions. Complement does not play a prominent role in the destruction of parasites by eosinophils.

(Choice D) Immediate (type I) hypersensitivity reactions are primarily mediated by mast cells and basophils. These cells possess Fc receptor-bound IgE on their membranes. Eosinophils contribute to late-phase type 1 hypersensitivity, but this is an allergic response that would not be protective against schistosomiasis.

(Choice E) Eosinophils can phagocytose parasitic antigens and present them in association with MHC class II molecules to stimulate helper T lymphocytes. In contrast, MHC class I antigen processing is involved in inducing a cytotoxic T lymphocyte response against intracellular pathogens (eg, viruses).

Educational objective:

Eosinophils play a role in host defense during multicellular parasitic infection. When stimulated by antibodies

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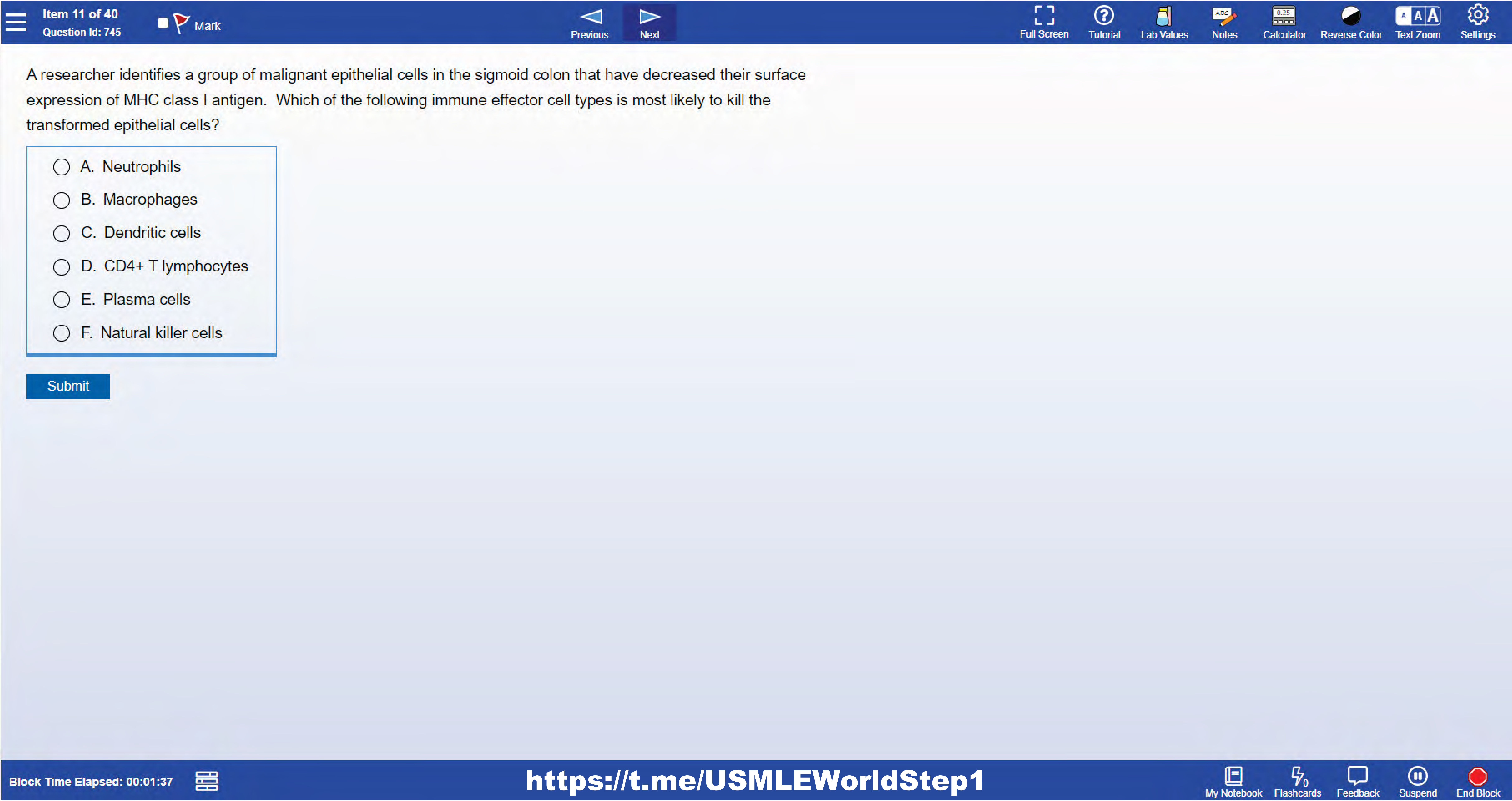
Educational objective:

Eosinophils play a role in host defense during multicellular parasitic infection. When stimulated by antibodies bound to a parasitic organism, they destroy the parasite via antibody-dependent cell-mediated cytotoxicity with enzymes from their cytoplasmic granules. Another function of eosinophils is regulation of type I hypersensitivity reactions.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A researcher identifies a group of malignant epithelial cells in the sigmoid colon that have decreased their surface expression of MHC class I antigen. Which of the following immune effector cell types is most likely to kill the transformed epithelial cells?

○ A. Neutrophils
○ B. Macrophages
○ C. Dendritic cells
○ D. CD4+ T lymphocytes
○ E. Plasma cells
○ F. Natural killer cells

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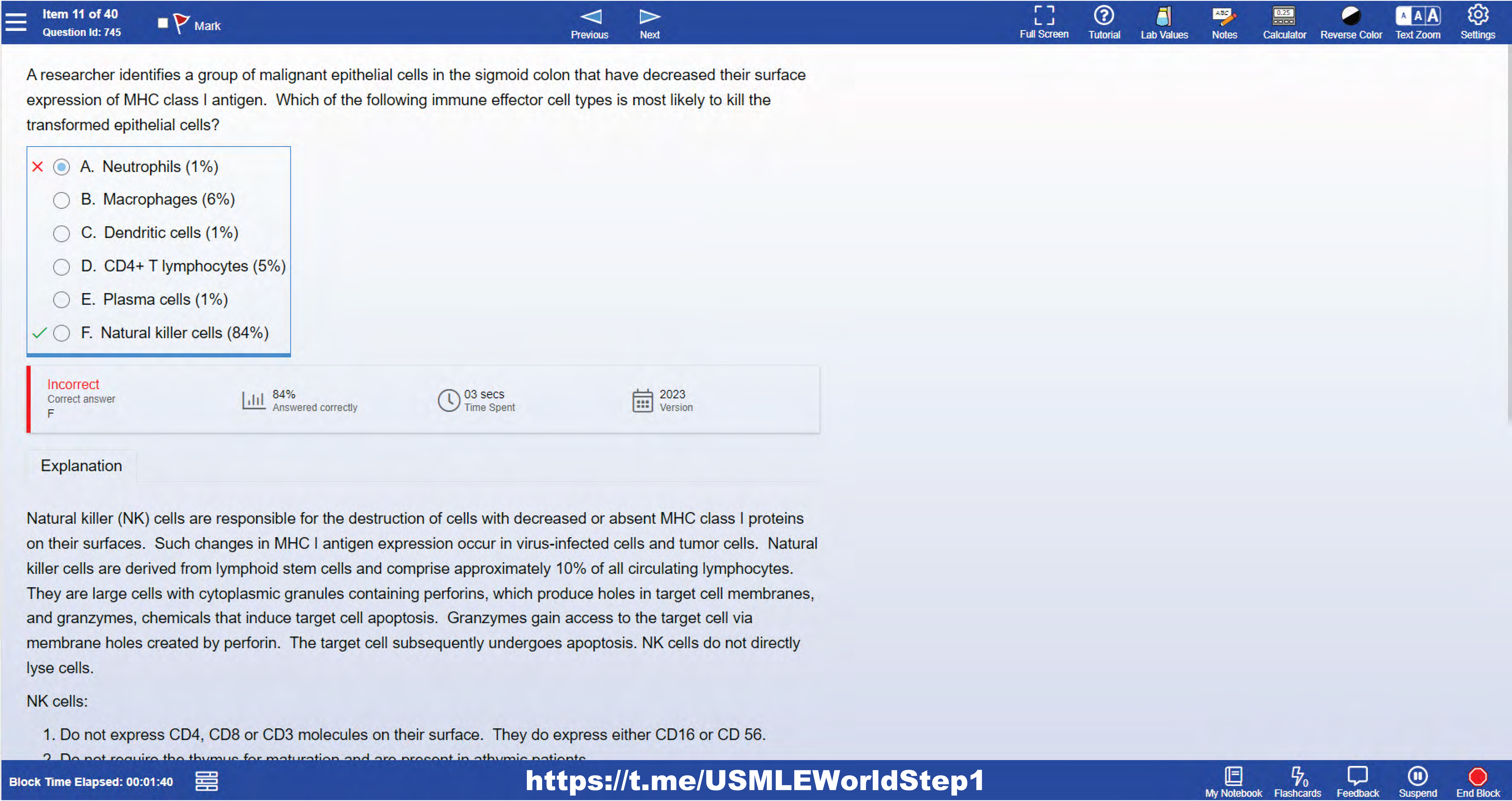
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A researcher identifies a group of malignant epithelial cells in the sigmoid colon that have decreased their surface expression of MHC class I antigen. Which of the following immune effector cell types is most likely to kill the transformed epithelial cells?

✗ ● A. Neutrophils (1%)
○ B. Macrophages (6%)
○ C. Dendritic cells (1%)
○ D. CD4+ T lymphocytes (5%)
○ E. Plasma cells (1%)
✓ ○ F. Natural killer cells (84%)

Incorrect
Correct answer
F

84%
Answered correctly

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Explanation

Natural killer (NK) cells are responsible for the destruction of cells with decreased or absent MHC class I proteins on their surfaces. Such changes in MHC I antigen expression occur in virus-infected cells and tumor cells. Natural killer cells are derived from lymphoid stem cells and comprise approximately 10% of all circulating lymphocytes. They are large cells with cytoplasmic granules containing perforins, which produce holes in target cell membranes, and granzymes, chemicals that induce target cell apoptosis. Granzymes gain access to the target cell via membrane holes created by perforin. The target cell subsequently undergoes apoptosis. NK cells do not directly lyse cells.

NK cells:

1. Do not express CD4, CD8 or CD3 molecules on their surface. They do express either CD16 or CD 56.
2. Do not require the thymus for maturation and are present in athymic patients.

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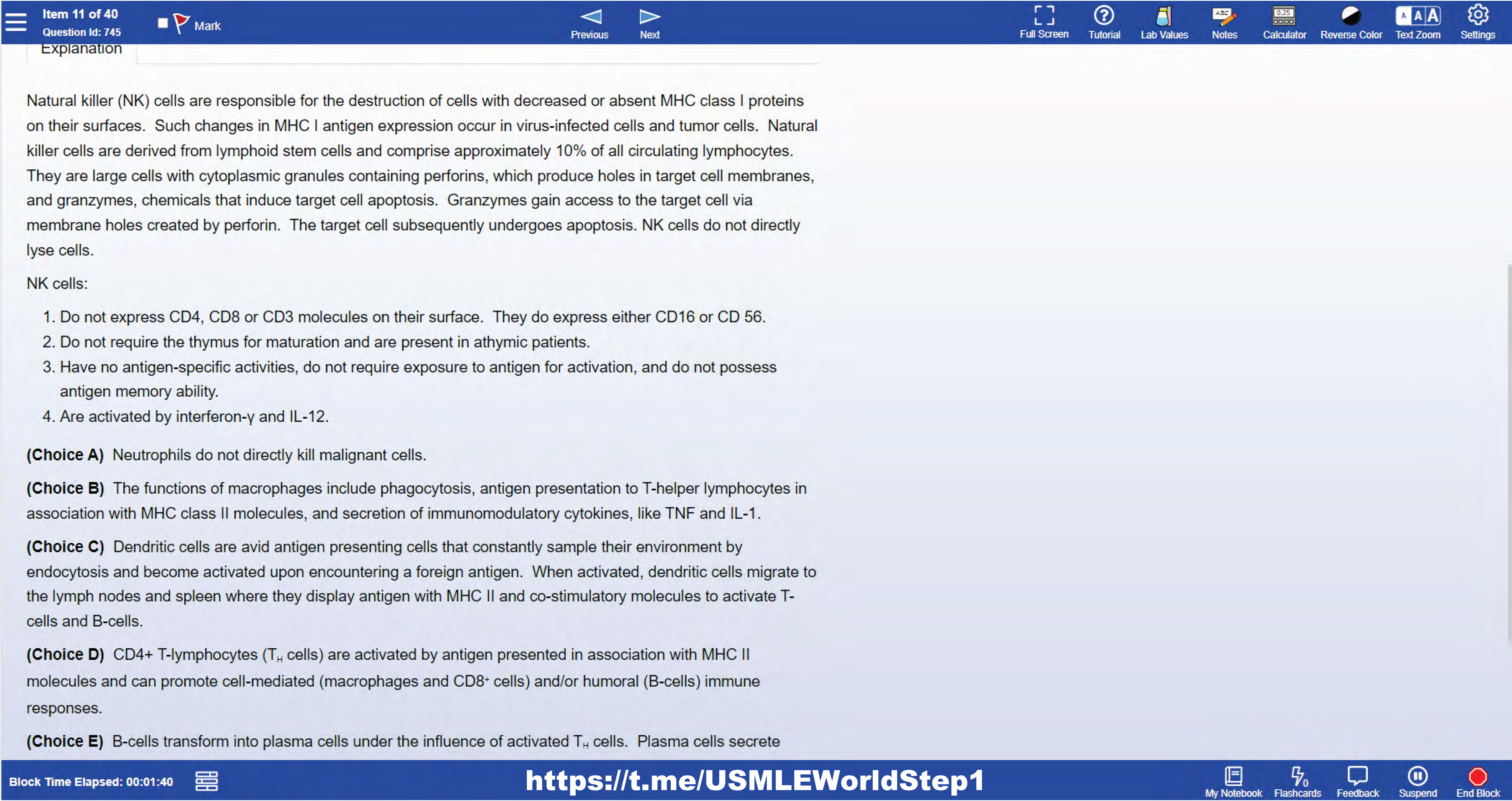
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Explanation
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NK cells:

1. Do not express CD4, CD8 or CD3 molecules on their surface. They do express either CD16 or CD 56.
2. Do not require the thymus for maturation and are present in athymic patients.
3. Have no antigen-specific activities, do not require exposure to antigen for activation, and do not possess antigen memory ability.
4. Are activated by interferon-γ and IL-12.

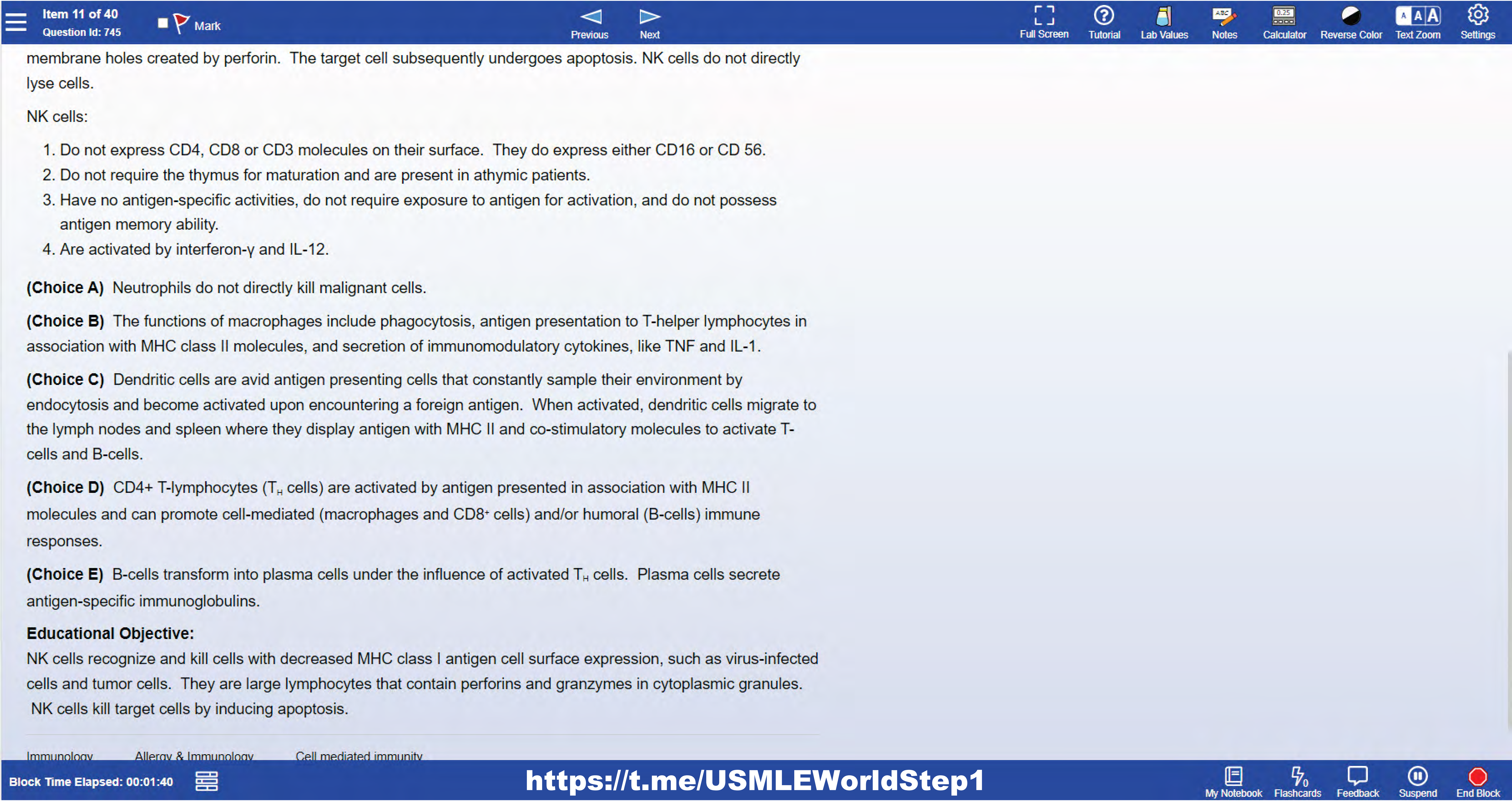
(Choice A) Neutrophils do not directly kill malignant cells.

(Choice B) The functions of macrophages include phagocytosis, antigen presentation to T-helper lymphocytes in association with MHC class II molecules, and secretion of immunomodulatory cytokines, like TNF and IL-1.

(Choice C) Dendritic cells are avid antigen presenting cells that constantly sample their environment by endocytosis and become activated upon encountering a foreign antigen. When activated, dendritic cells migrate to the lymph nodes and spleen where they display antigen with MHC II and co-stimulatory molecules to activate T-cells and B-cells.

(Choice D) CD4+ T-lymphocytes (T_H cells) are activated by antigen presented in association with MHC II molecules and can promote cell-mediated (macrophages and $CD8^+$ cells) and/or humoral (B-cells) immune responses.

(Choice E) B-cells transform into plasma cells under the influence of activated T_H cells. Plasma cells secrete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membrane holes created by perforin. The target cell subsequently undergoes apoptosis. NK cells do not directly lyse cells.

NK cells:

1. Do not express CD4, CD8 or CD3 molecules on their surface. They do express either CD16 or CD 56.
2. Do not require the thymus for maturation and are present in athymic patients.
3. Have no antigen-specific activities, do not require exposure to antigen for activation, and do not possess antigen memory ability.
4. Are activated by interferon-γ and IL-12.

(Choice A) Neutrophils do not directly kill malignant cells.

(Choice B) The functions of macrophages include phagocytosis, antigen presentation to T-helper lymphocytes in association with MHC class II molecules, and secretion of immunomodulatory cytokines, like TNF and IL-1.

(Choice C) Dendritic cells are avid antigen presenting cells that constantly sample their environment by endocytosis and become activated upon encountering a foreign antigen. When activated, dendritic cells migrate to the lymph nodes and spleen where they display antigen with MHC II and co-stimulatory molecules to activate T-cells and B-cells.

(Choice D) CD4+ T-lymphocytes (T_H cells) are activated by antigen presented in association with MHC II molecules and can promote cell-mediated (macrophages and $CD8^+$ cells) and/or humoral (B-cells) immune responses.

(Choice E) B-cells transform into plasma cells under the influence of activated T_H cells. Plasma cells secrete antigen-specific immunoglobulins.

Educational Objective:

NK cells recognize and kill cells with decreased MHC class I antigen cell surface expression, such as virus-infected cells and tumor cells. They are large lymphocytes that contain perforins and granzymes in cytoplasmic granules. NK cells kill target cells by inducing apoptosis.

Immunology Allergy & Immunology Cell mediated immunity

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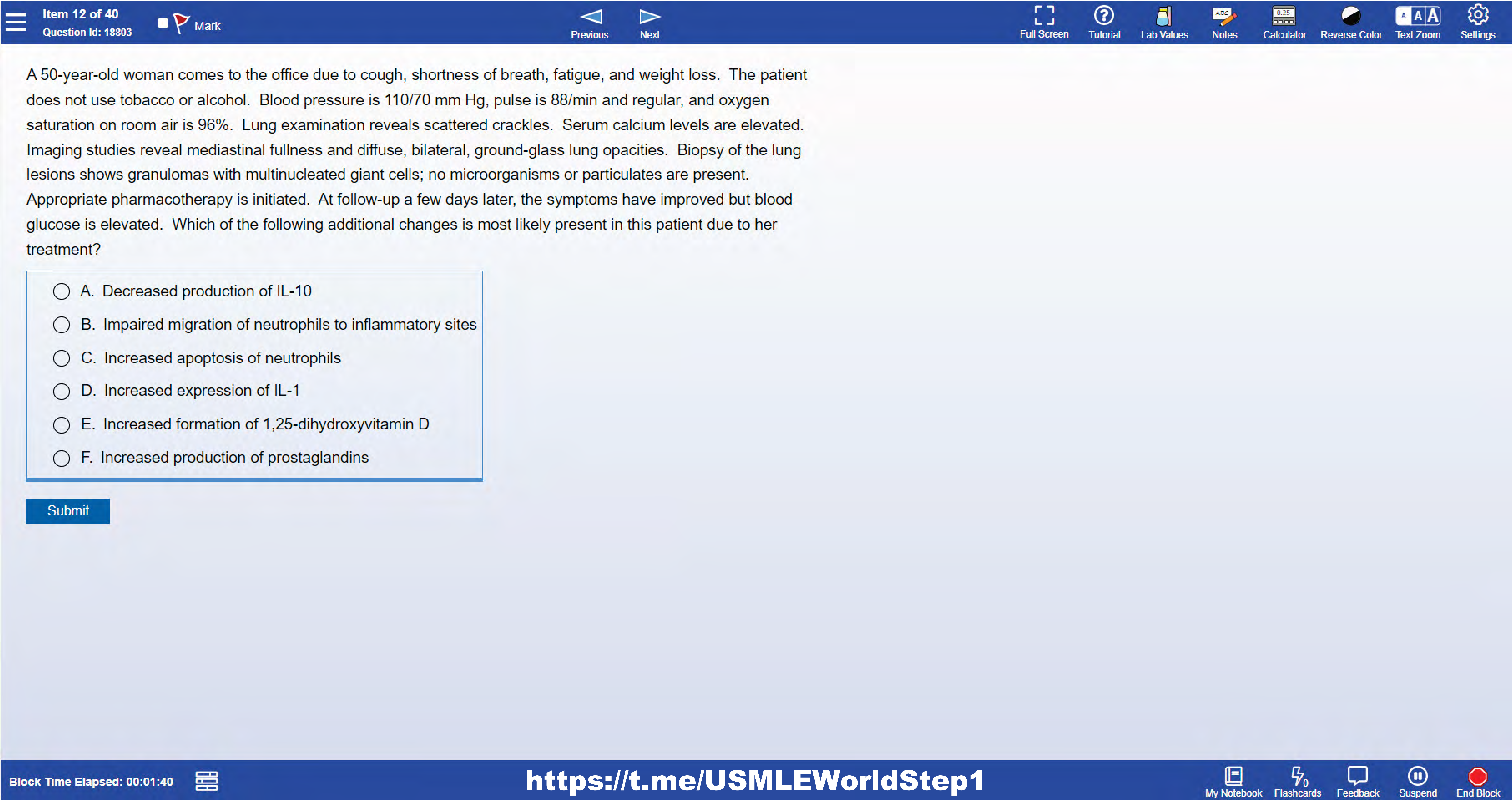
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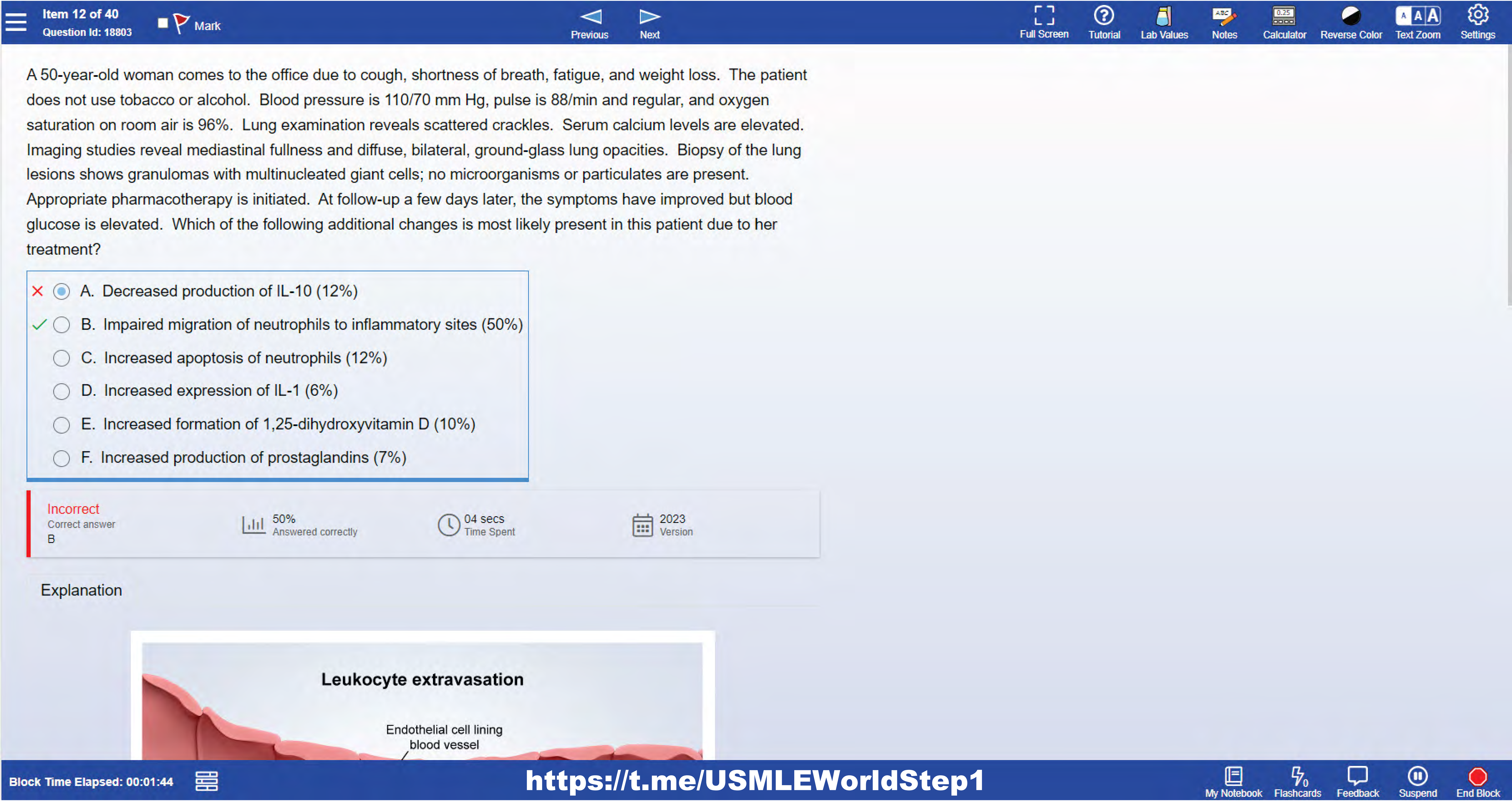
A 50-year-old woman comes to the office due to cough, shortness of breath, fatigue, and weight loss. The patient does not use tobacco or alcohol. Blood pressure is 110/70 mm Hg, pulse is 88/min and regular, and oxygen saturation on room air is 96%. Lung examination reveals scattered crackles. Serum calcium levels are elevated. Imaging studies reveal mediastinal fullness and diffuse, bilateral, ground-glass lung opacities. Biopsy of the lung lesions shows granulomas with multinucleated giant cells; no microorganisms or particulates are present. Appropriate pharmacotherapy is initiated. At follow-up a few days later, the symptoms have improved but blood glucose is elevated. Which of the following additional changes is most likely present in this patient due to her treatment?

- ○ A. Decreased production of IL-10
- ○ B. Impaired migration of neutrophils to inflammatory sites
- ○ C. Increased apoptosis of neutrophils
- ○ D. Increased expression of IL-1
- ○ E. Increased formation of 1,25-dihydroxyvitamin D
- ○ F. Increased production of prostaglandins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A 50-year-old woman comes to the office due to cough, shortness of breath, fatigue, and weight loss. The patient does not use tobacco or alcohol. Blood pressure is 110/70 mm Hg, pulse is 88/min and regular, and oxygen saturation on room air is 96%. Lung examination reveals scattered crackles. Serum calcium levels are elevated. Imaging studies reveal mediastinal fullness and diffuse, bilateral, ground-glass lung opacities. Biopsy of the lung lesions shows granulomas with multinucleated giant cells; no microorganisms or particulates are present. Appropriate pharmacotherapy is initiated. At follow-up a few days later, the symptoms have improved but blood glucose is elevated. Which of the following additional changes is most likely present in this patient due to her treatment?

- ✗ ● A. Decreased production of IL-10 (12%)
- ✓ ○ B. Impaired migration of neutrophils to inflammatory sites (50%)
- ○ C. Increased apoptosis of neutrophils (12%)
- ○ D. Increased expression of IL-1 (6%)
- ○ E. Increased formation of 1,25-dihydroxyvitamin D (10%)
- ○ F. Increased production of prostaglandins (7%)

Incorrect
Correct answer
B

50%
Answered correctly

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Explanation

Leukocyte extravasation

Endothelial cell lining
blood vessel
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glucose is elevated. Which of the following additional changes is most likely present in this patient due to her treatm

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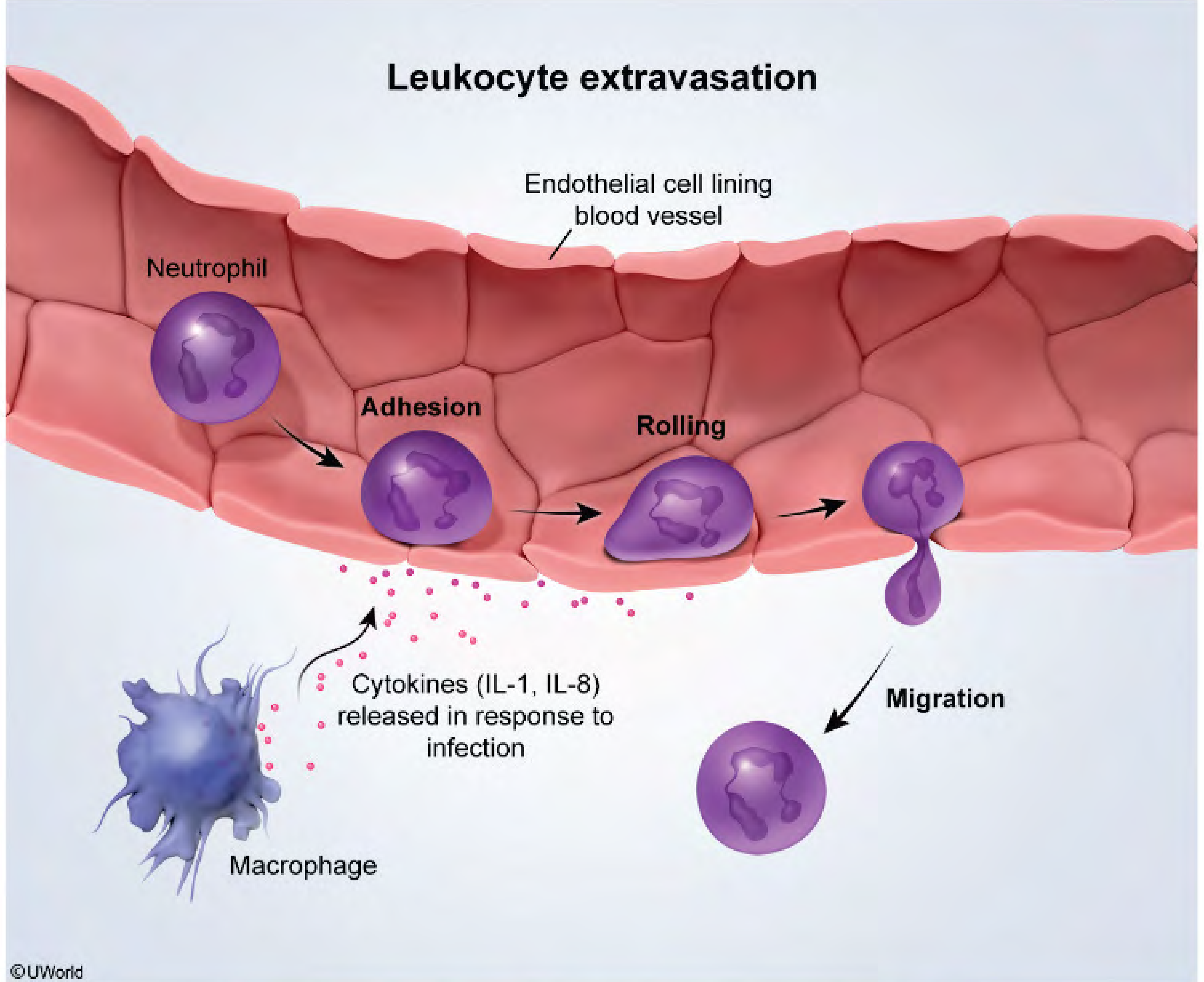
Leukocyte extravasation
Endothelial cell lining blood vessel
Neutrophil
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Cytokines (IL-1, IL-8) released in response to infection
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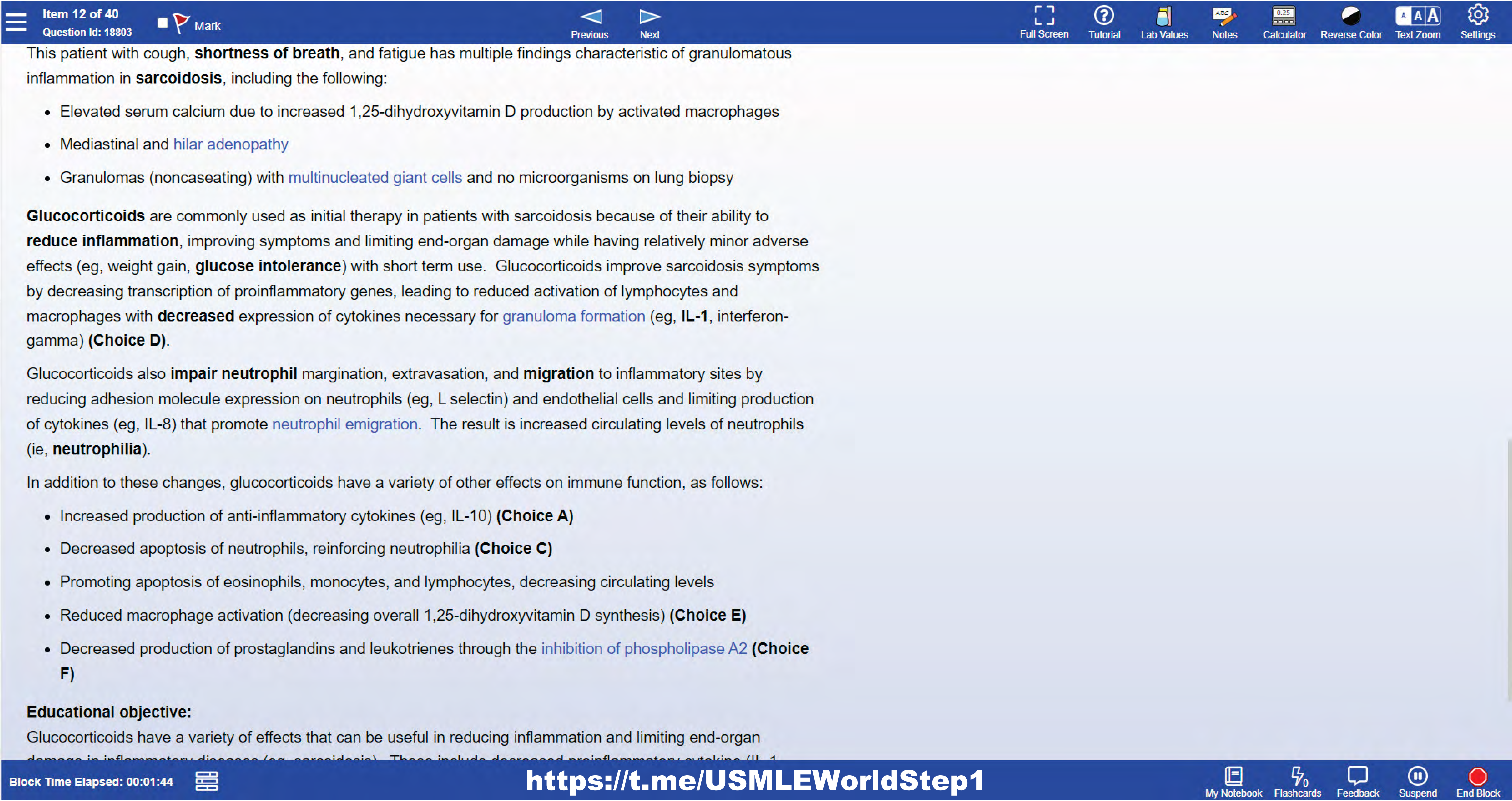


This patient with cough, **shortness of breath**, and fatigue has multiple findings characteristic of granulomatous inflammation in **sarcoidosis**, including the following:

- Elevated serum calcium due to increased 1,25-dihydroxyvitamin D production by activated macrophages
- Mediastinal and hilar adenopathy
- Granulomas (noncaseating) with multinucleated giant cells and no microorganisms on lung biopsy

Glucocorticoids are commonly used as initial therapy in patients with sarcoidosis because of their ability to **reduce inflammation**, improving symptoms and limiting end-organ damage while having relatively minor adverse effects (eg, weight gain, **glucose intolerance**) with short term use. Glucocorticoids improve sarcoidosis symptoms by decreasing transcription of proinflammatory genes, leading to reduced activation of lymphocytes and macrophages with **decreased** expression of cytokines necessary for granuloma formation (eg, **IL-1**, interferon-gamma) **(Choice D)**.

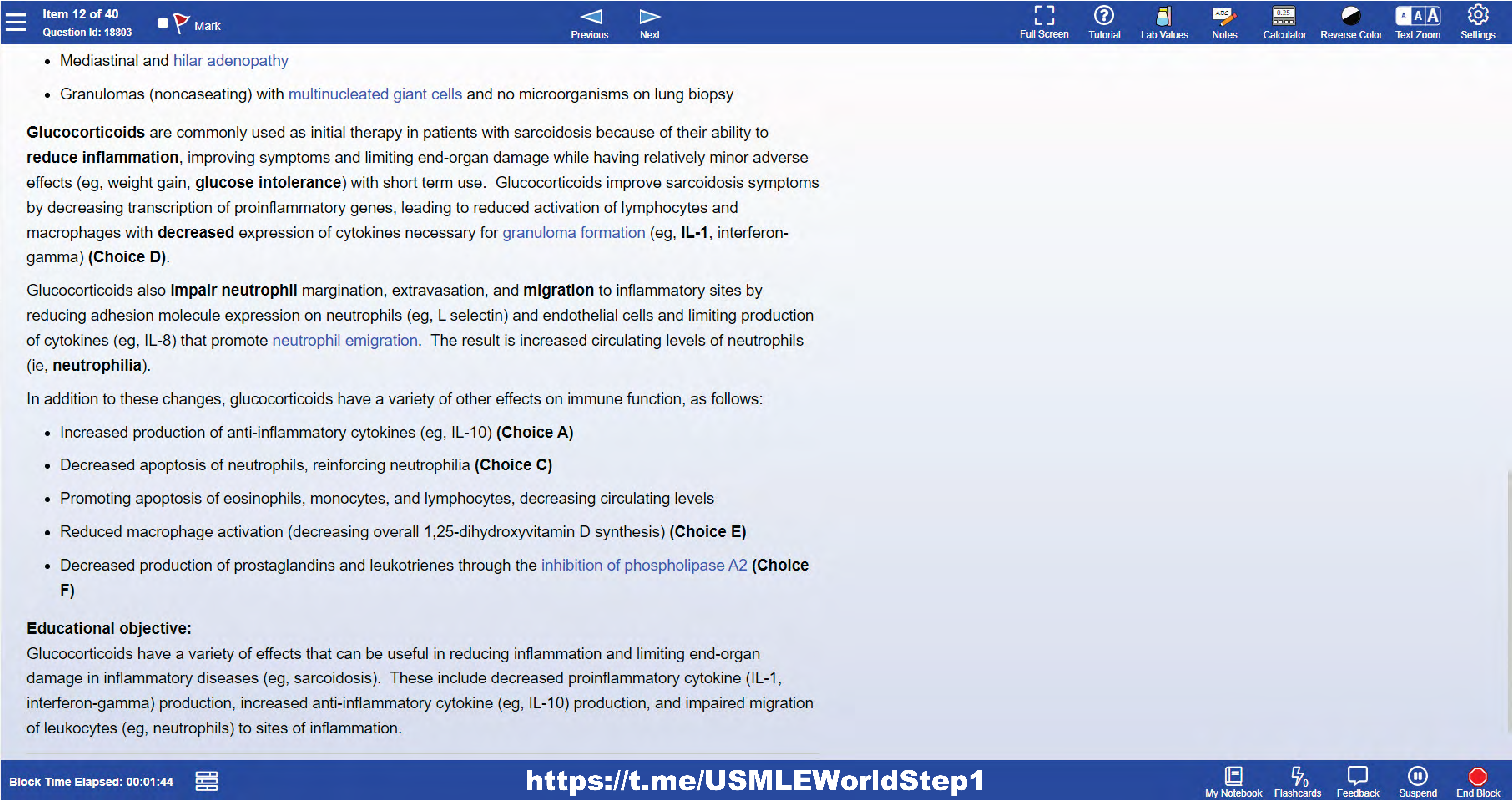
Glucocorticoids also **impair neutrophil** margination, extravasation, and **migration** to inflammatory sites by reducing adhesion molecule expression on neutrophils (eg, L selectin) and endothelial cells and limiting production of cytokines (eg, IL-8) that promote neutrophil emigration. The result is increased circulating levels of neutrophils (ie, **neutrophilia**).

In addition to these changes, glucocorticoids have a variety of other effects on immune function, as follows:

- Increased production of anti-inflammatory cytokines (eg, IL-10) **(Choice A)**
- Decreased apoptosis of neutrophils, reinforcing neutrophilia **(Choice C)**
- Promoting apoptosis of eosinophils, monocytes, and lymphocytes, decreasing circulating levels
- Reduced macrophage activation (decreasing overall 1,25-dihydroxyvitamin D synthesis) **(Choice E)**
- Decreased production of prostaglandins and leukotrienes through the inhibition of phospholipase A2 **(Choice F)**

Educational objective:

Glucocorticoids have a variety of effects that can be useful in reducing inflammation and limiting end-organ damage in inflammatory diseases (eg, sarcoidosis). These include decreased proinflammatory cytokine (IL-1



- Mediastinal and hilar adenopathy
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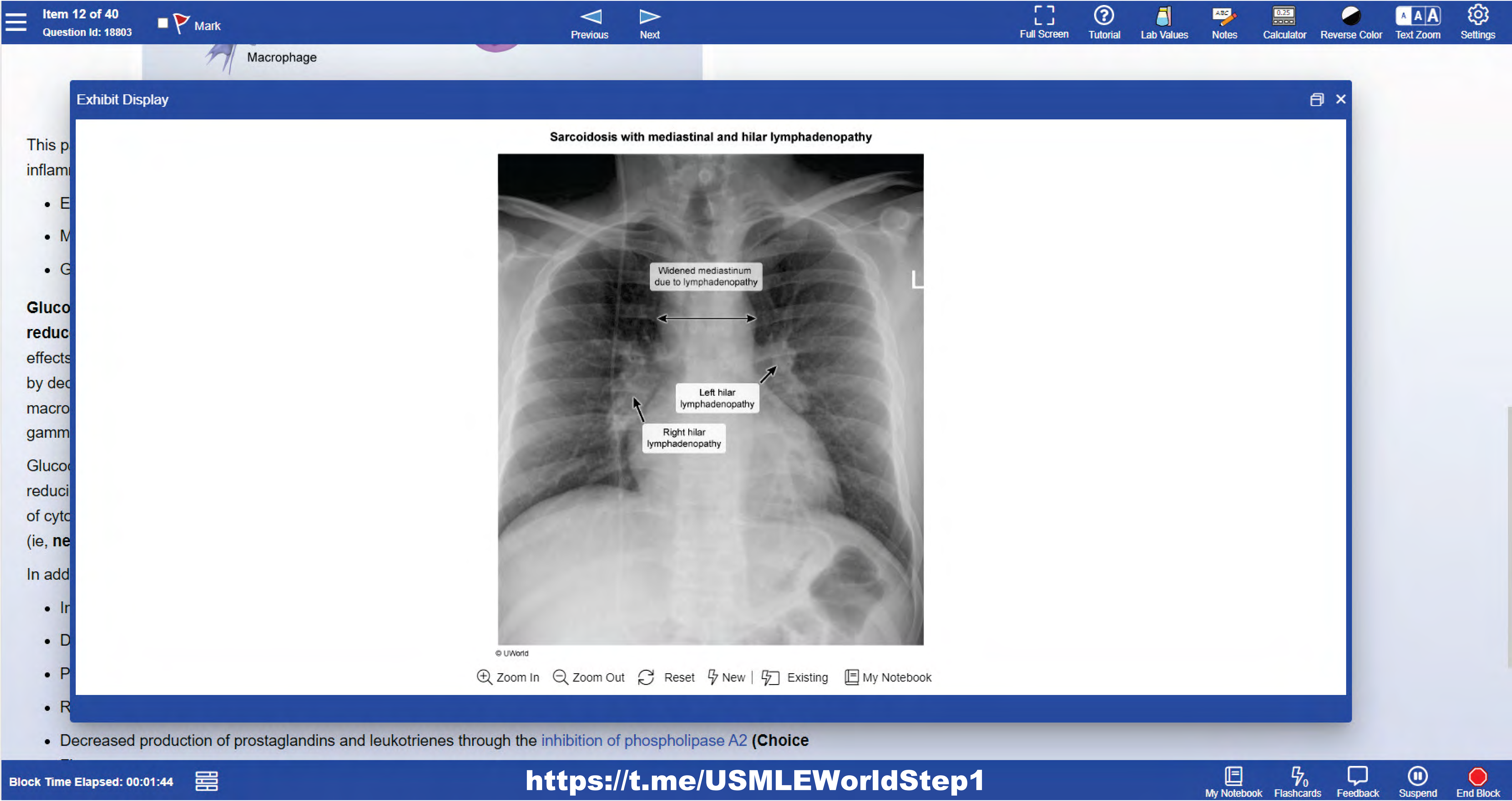
- Decreased apoptosis of neutrophils, reinforcing neutrophilia **(Choice C)**
- Promoting apoptosis of eosinophils, monocytes, and lymphocytes, decreasing circulating levels
- Reduced macrophage activation (decreasing overall 1,25-dihydroxyvitamin D synthesis) **(Choice E)**
- Decreased production of prostaglandins and leukotrienes through the inhibition of phospholipase A2 **(Choice F)**

Educational objective:
Glucocorticoids have a variety of effects that can be useful in reducing inflammation and limiting end-organ damage in inflammatory diseases (eg, sarcoidosis). These include decreased proinflammatory cytokine (IL-1, interferon-gamma) production, increased anti-inflammatory cytokine (eg, IL-10) production, and impaired migration of leukocytes (eg, neutrophils) to sites of inflammation.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Right hilar lymphadenopathy
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Sarcoidosis with mediastinal and hilar lymphadenopathy

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- Decreased production of prostaglandins and leukotrienes through the inhibition of phospholipase A2 **(Choice**

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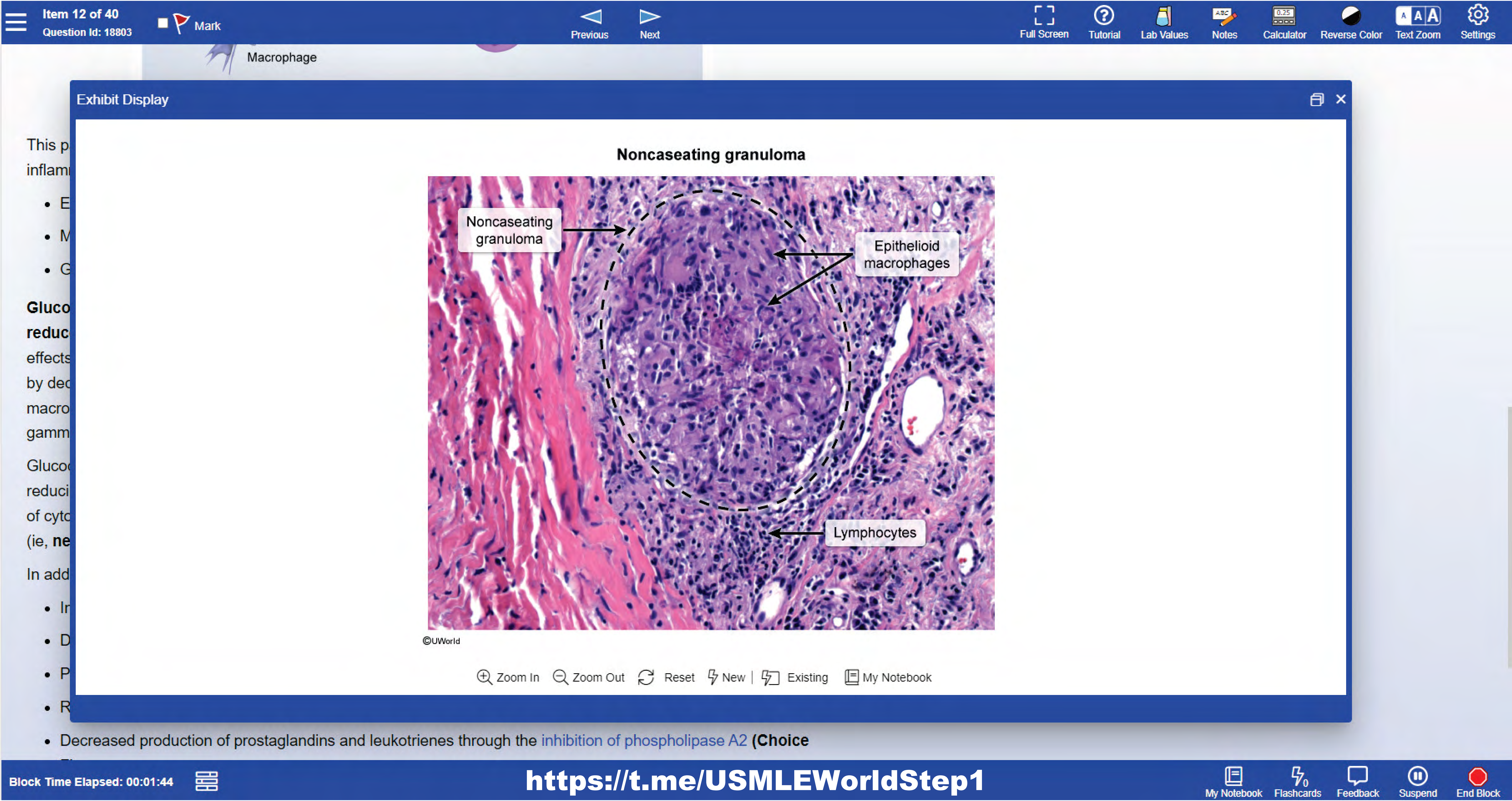
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- Decreased production of prostaglandins and leukotrienes through the inhibition of phospholipase A2 **(Choice**

Noncaseating granuloma

Noncaseating granuloma
Epithelioid macrophages
Lymphocytes

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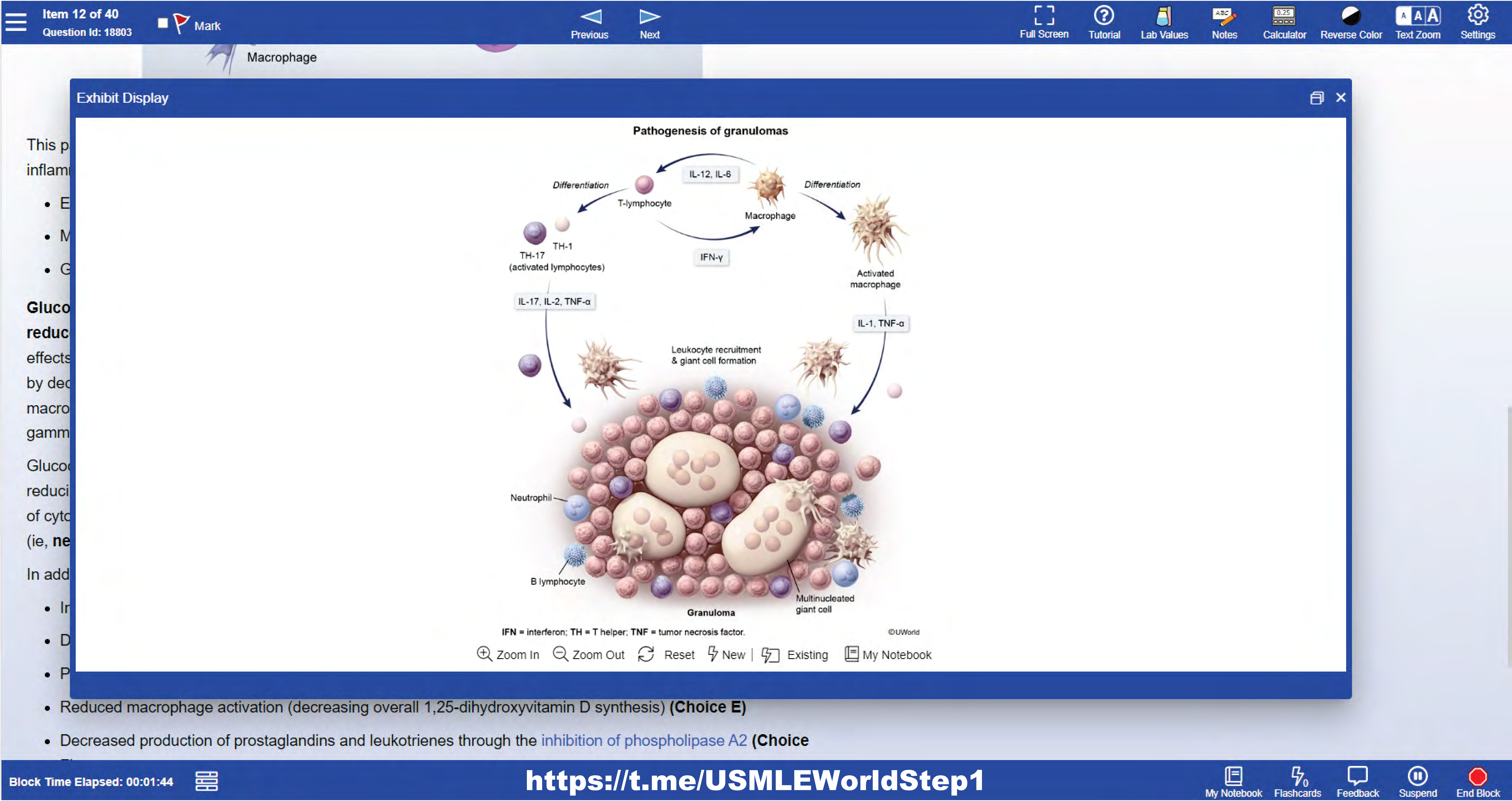
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Differentiation
T-lymphocyte
IL-12, IL-6
Macrophage
Differentiation
TH-1
TH-17
(activated lymphocytes)
IFN-γ
Activated
macrophage
IL-17, IL-2, TNF-α
IL-1, TNF-α
Leukocyte recruitment
& giant cell formation
Neutrophil
B lymphocyte
Granuloma
Multinucleated
giant cell
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Pathogenesis of granulomas

IFN = interferon; TH = T helper; TNF = tumor necrosis factor.

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- Reduced macrophage activation (decreasing overall 1,25-dihydroxyvitamin D synthesis) **(Choice E)**
- Decreased production of prostaglandins and leukotrienes through the inhibition of phospholipase A2 **(Choice**

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- Mediastinal and hilar adenopathy
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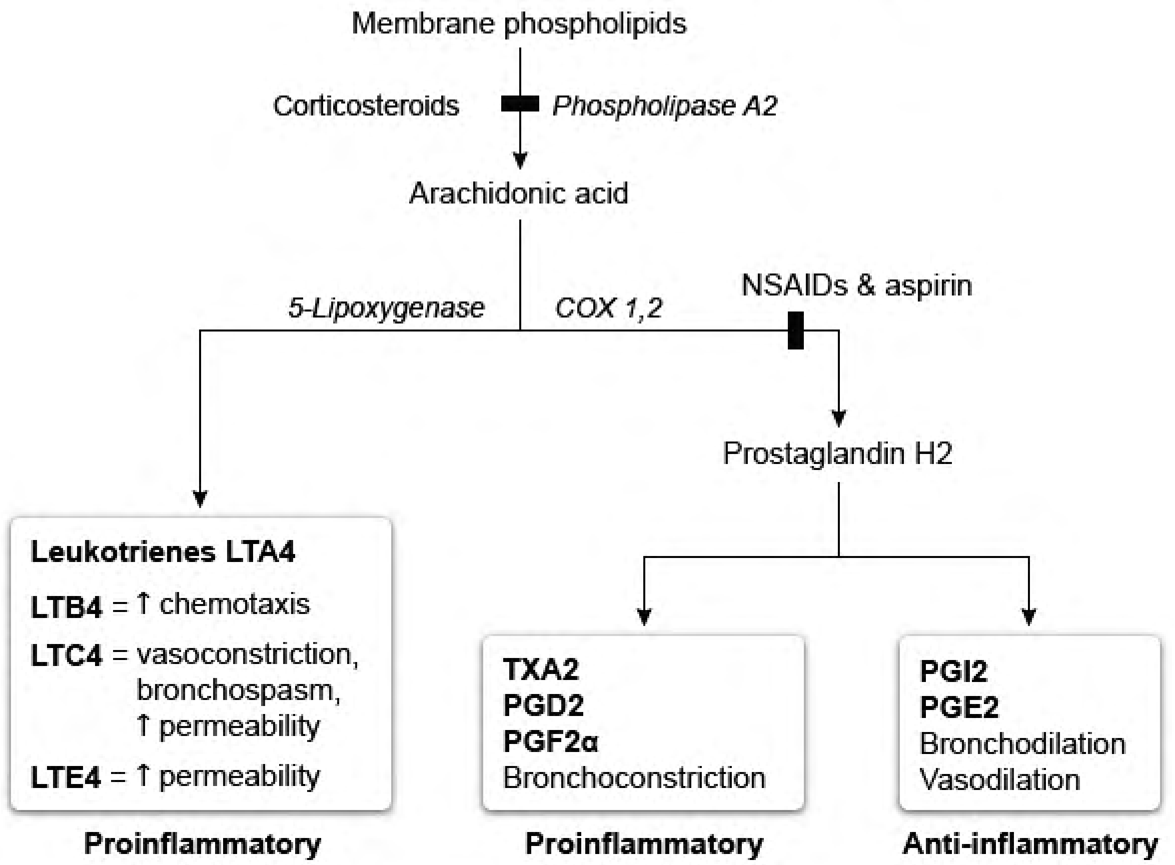
Arachidonic acid metabolic pathways


Membrane phospholipids
Corticosteroids
Phospholipase A2
Arachidonic acid
5-Lipoxygenase
COX 1,2
NSAIDs & aspirin
Prostaglandin H2
Leukotrienes LTA4
LTB4 = ↑ chemotaxis
LTC4 = vasoconstriction, bronchospasm, ↑ permeability
LTE4 = ↑ permeability
TXA2
PGD2
PGF2α
Bronchoconstriction
PGI2
PGE2
Bronchodilation
Vasodilation
Proinflammatory
Proinflammatory
Anti-inflammatory

COX = cyclooxygenase-2; **NSAIDs** = nonsteroidal anti-inflammatory drugs;
PG = prostaglandin; **TXA** = thromboxane.

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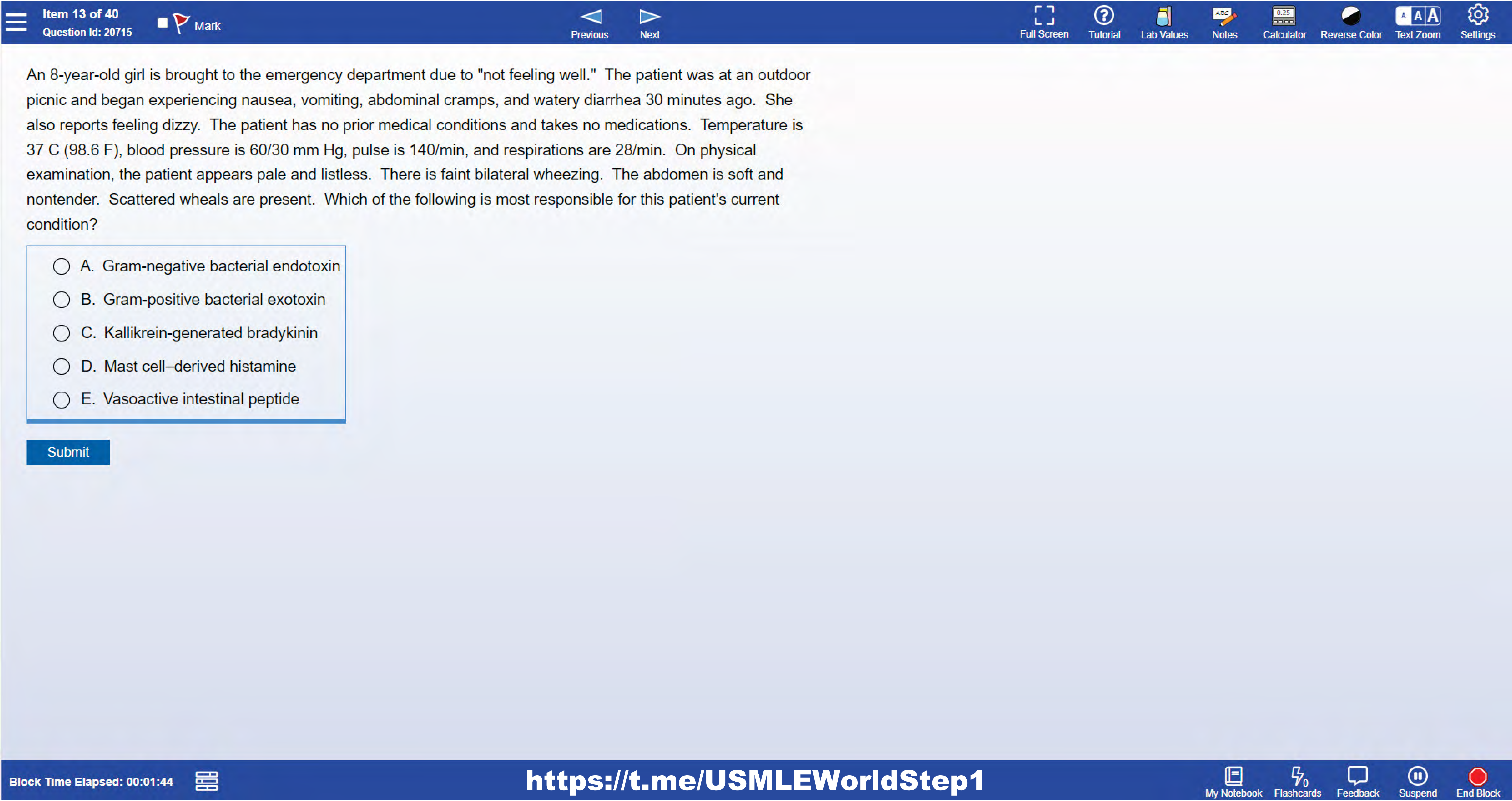
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An 8-year-old girl is brought to the emergency department due to "not feeling well." The patient was at an outdoor picnic and began experiencing nausea, vomiting, abdominal cramps, and watery diarrhea 30 minutes ago. She also reports feeling dizzy. The patient has no prior medical conditions and takes no medications. Temperature is 37 C (98.6 F), blood pressure is 60/30 mm Hg, pulse is 140/min, and respirations are 28/min. On physical examination, the patient appears pale and listless. There is faint bilateral wheezing. The abdomen is soft and nontender. Scattered wheals are present. Which of the following is most responsible for this patient's current condition?

- ○ A. Gram-negative bacterial endotoxin
- ○ B. Gram-positive bacterial exotoxin
- ○ C. Kallikrein-generated bradykinin
- ○ D. Mast cell–derived histamine
- ○ E. Vasoactive intestinal peptide

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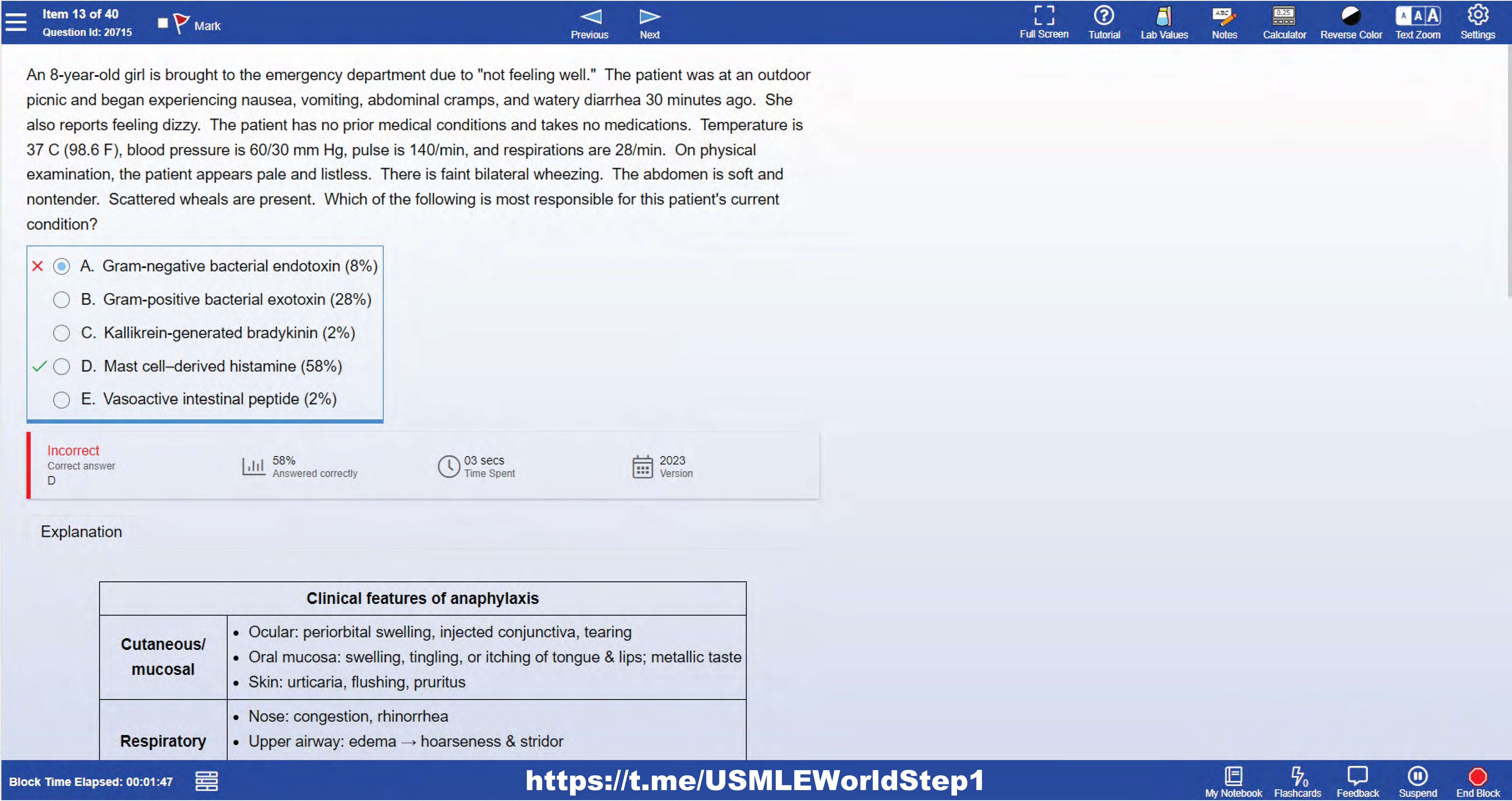
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- ✗ ● A. Gram-negative bacterial endotoxin (8%)
- ○ B. Gram-positive bacterial exotoxin (28%)
- ○ C. Kallikrein-generated bradykinin (2%)
- ✓ ○ D. Mast cell–derived histamine (58%)
- ○ E. Vasoactive intestinal peptide (2%)

Incorrect
Correct answer
D

58%
Answered correctly

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Explanation

Clinical features of anaphylaxis	
Cutaneous/ mucosal	• Ocular: periorbital swelling, injected conjunctiva, tearing • Oral mucosa: swelling, tingling, or itching of tongue & lips; metallic taste • Skin: urticaria, flushing, pruritus
Respiratory	• Nose: congestion, rhinorrhea • Upper airway: edema → hoarseness & stridor

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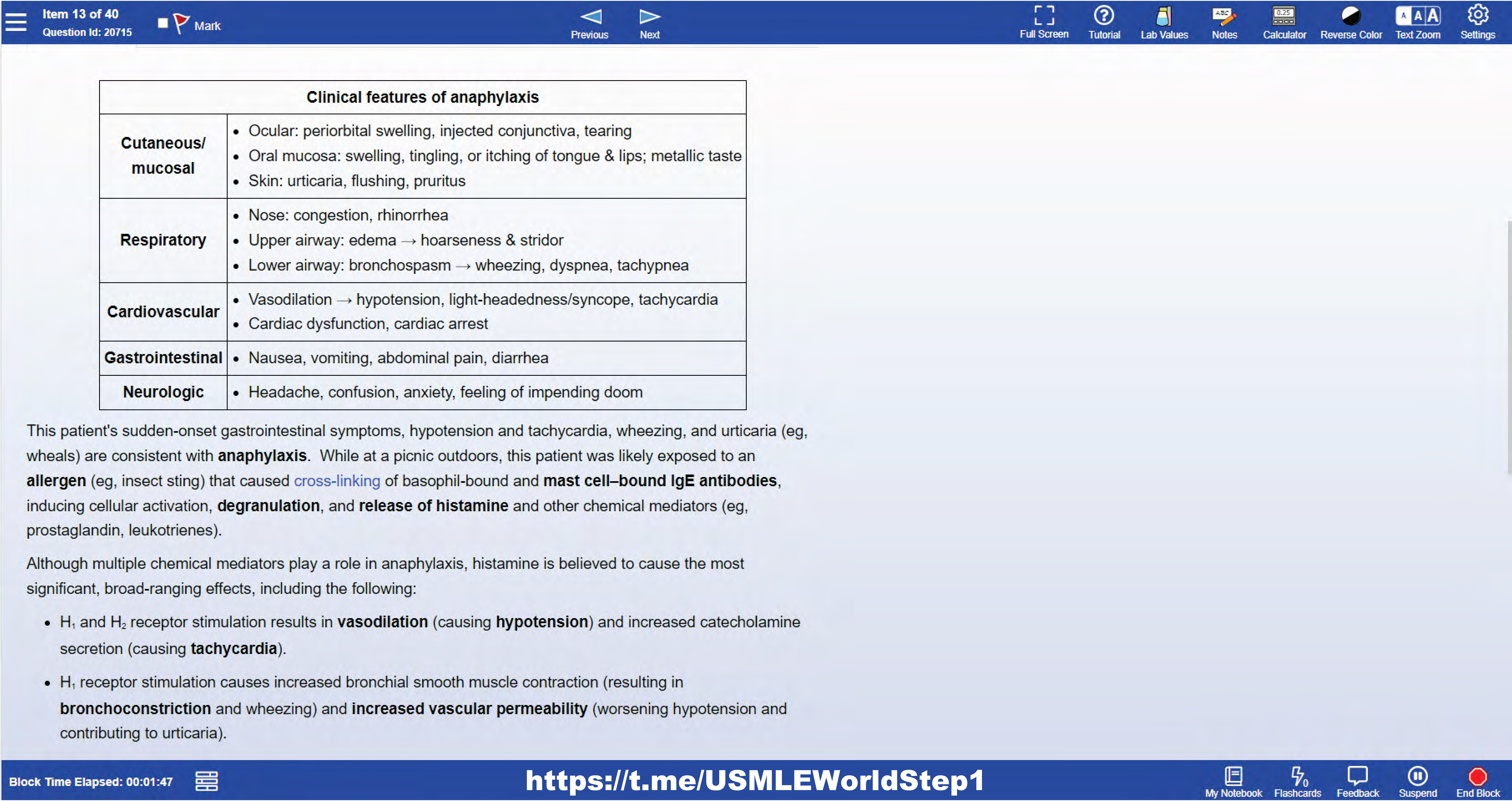
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Clinical features of anaphylaxis	
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Respiratory	• Nose: congestion, rhinorrhea • Upper airway: edema → hoarseness & stridor • Lower airway: bronchospasm → wheezing, dyspnea, tachypnea
Cardiovascular	• Vasodilation → hypotension, light-headedness/syncope, tachycardia • Cardiac dysfunction, cardiac arrest
Gastrointestinal	• Nausea, vomiting, abdominal pain, diarrhea
Neurologic	• Headache, confusion, anxiety, feeling of impending doom

This patient's sudden-onset gastrointestinal symptoms, hypotension and tachycardia, wheezing, and urticaria (eg, wheals) are consistent with **anaphylaxis**. While at a picnic outdoors, this patient was likely exposed to an **allergen** (eg, insect sting) that caused cross-linking of basophil-bound and **mast cell–bound IgE antibodies**, inducing cellular activation, **degranulation**, and **release of histamine** and other chemical mediators (eg, prostaglandin, leukotrienes).

Although multiple chemical mediators play a role in anaphylaxis, histamine is believed to cause the most significant, broad-ranging effects, including the following:

- H_1 and H_2 receptor stimulation results in **vasodilation** (causing **hypotension**) and increased catecholamine secretion (causing **tachycardia**).
- H_1 receptor stimulation causes increased bronchial smooth muscle contraction (resulting in **bronchoconstriction** and wheezing) and **increased vascular permeability** (worsening hypotension and contributing to urticaria).

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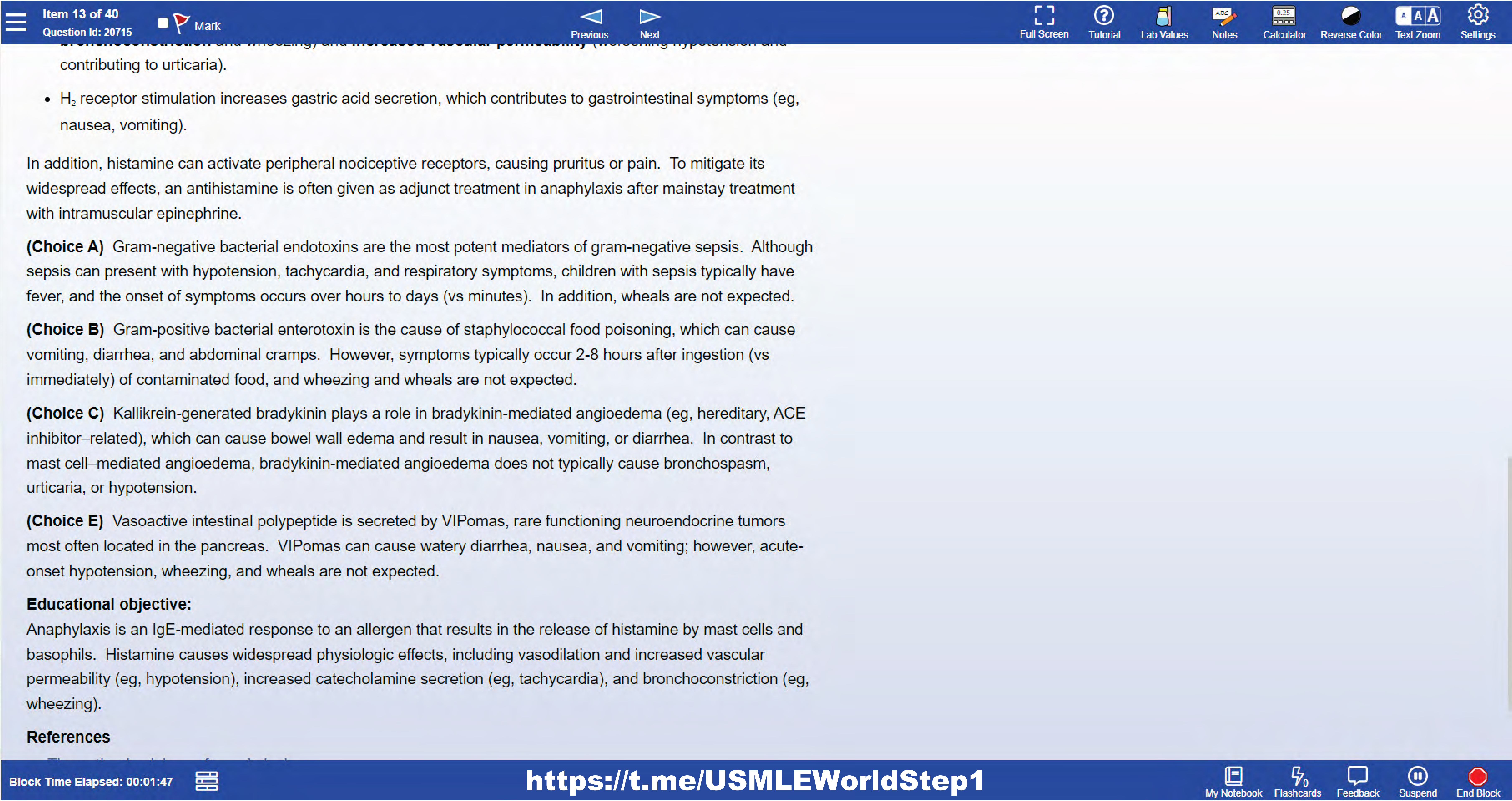

contributing to urticaria).

- H_2 receptor stimulation increases gastric acid secretion, which contributes to gastrointestinal symptoms (eg, nausea, vomiting).

In addition, histamine can activate peripheral nociceptive receptors, causing pruritus or pain. To mitigate its widespread effects, an antihistamine is often given as adjunct treatment in anaphylaxis after mainstay treatment with intramuscular epinephrine.

(Choice A) Gram-negative bacterial endotoxins are the most potent mediators of gram-negative sepsis. Although sepsis can present with hypotension, tachycardia, and respiratory symptoms, children with sepsis typically have fever, and the onset of symptoms occurs over hours to days (vs minutes). In addition, wheals are not expected.

(Choice B) Gram-positive bacterial enterotoxin is the cause of staphylococcal food poisoning, which can cause vomiting, diarrhea, and abdominal cramps. However, symptoms typically occur 2-8 hours after ingestion (vs immediately) of contaminated food, and wheezing and wheals are not expected.

(Choice C) Kallikrein-generated bradykinin plays a role in bradykinin-mediated angioedema (eg, hereditary, ACE inhibitor–related), which can cause bowel wall edema and result in nausea, vomiting, or diarrhea. In contrast to mast cell–mediated angioedema, bradykinin-mediated angioedema does not typically cause bronchospasm, urticaria, or hypotension.

(Choice E) Vasoactive intestinal polypeptide is secreted by VIPomas, rare functioning neuroendocrine tumors most often located in the pancreas. VIPomas can cause watery diarrhea, nausea, and vomiting; however, acute-onset hypotension, wheezing, and wheals are not expected.

Educational objective:

Anaphylaxis is an IgE-mediated response to an allergen that results in the release of histamine by mast cells and basophils. Histamine causes widespread physiologic effects, including vasodilation and increased vascular permeability (eg, hypotension), increased catecholamine secretion (eg, tachycardia), and bronchoconstriction (eg, wheezing).

References

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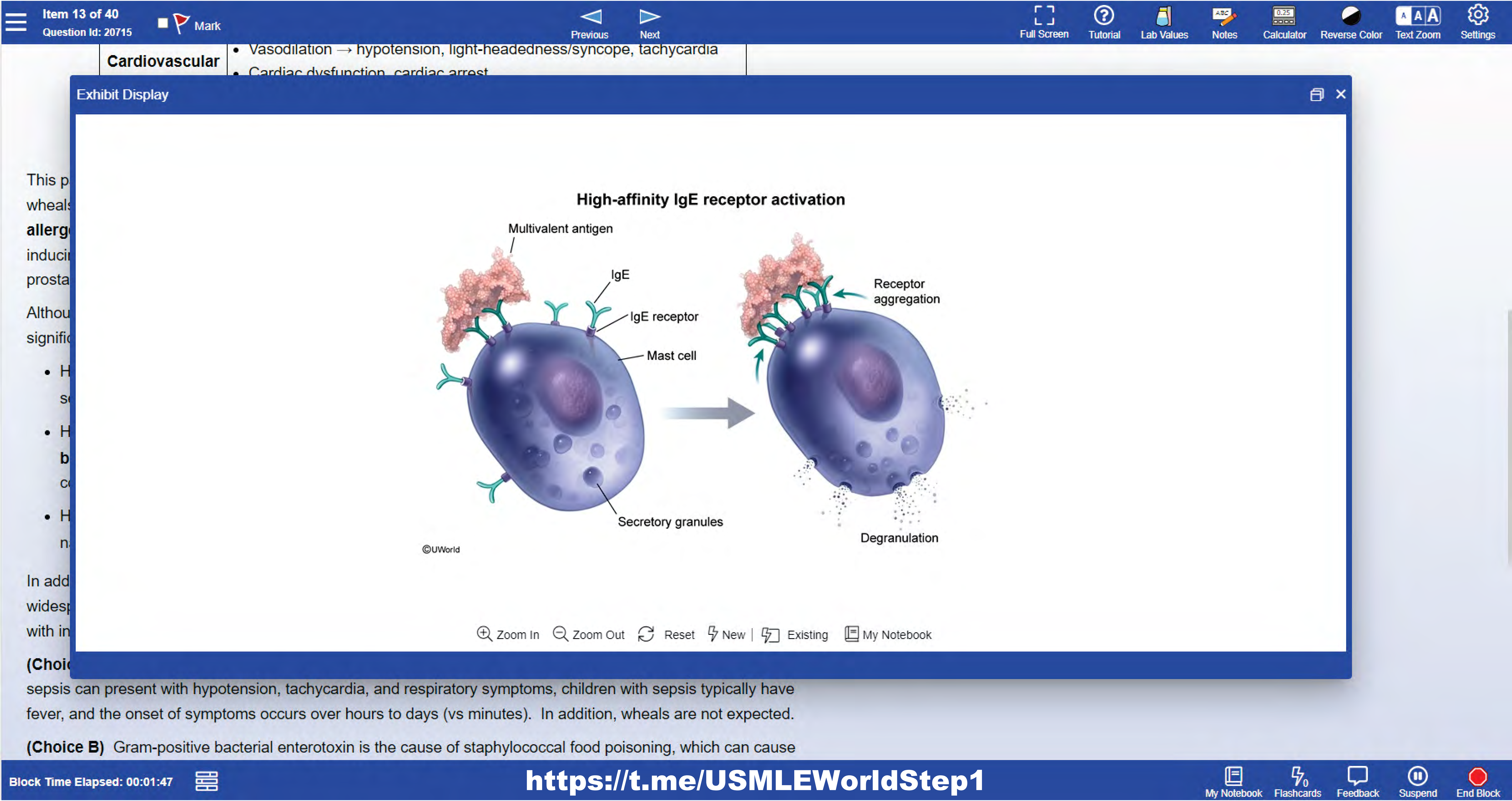
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High-affinity IgE receptor activation
Multivalent antigen
IgE
IgE receptor
Mast cell
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Receptor aggregation
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Cardiovascular	- Vasodilation → hypotension, light-headedness/syncope, tachycardia - Cardiac dysfunction, cardiac arrest

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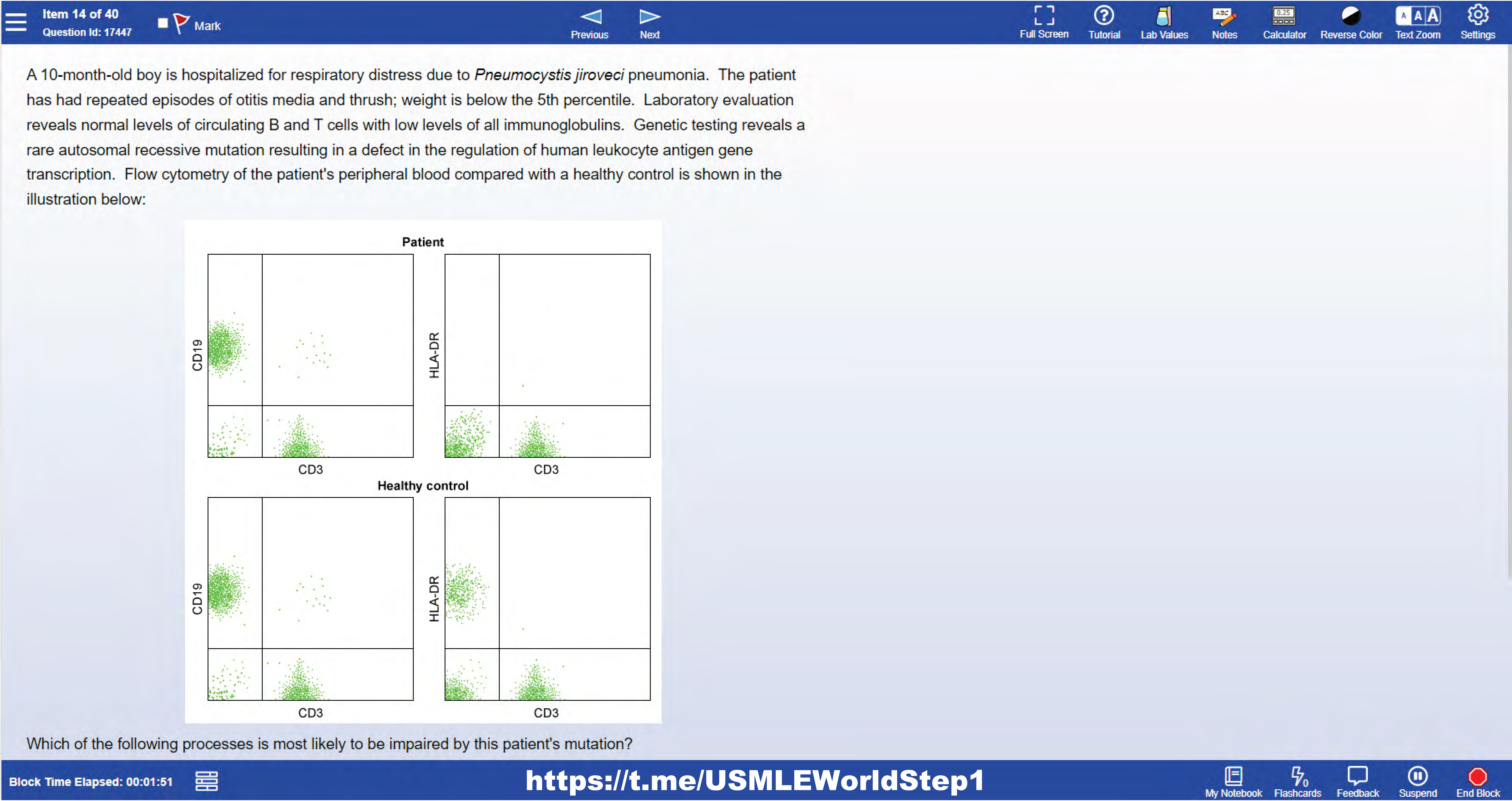
sepsis can present with hypotension, tachycardia, and respiratory symptoms, children with sepsis typically have fever, and the onset of symptoms occurs over hours to days (vs minutes). In addition, wheals are not expected.

(Choice B) Gram-positive bacterial enterotoxin is the cause of staphylococcal food poisoning, which can cause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A 10-month-old boy is hospitalized for respiratory distress due to *Pneumocystis jiroveci* pneumonia. The patient has had repeated episodes of otitis media and thrush; weight is below the 5th percentile. Laboratory evaluation reveals normal levels of circulating B and T cells with low levels of all immunoglobulins. Genetic testing reveals a rare autosomal recessive mutation resulting in a defect in the regulation of human leukocyte antigen gene transcription. Flow cytometry of the patient's peripheral blood compared with a healthy control is shown in the illustration below:

Patient
CD19
CD3
HLA-DR
CD3
Healthy control
CD19
CD3
HLA-DR
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Which of the following processes is most likely to be impaired by this patient's mutation?

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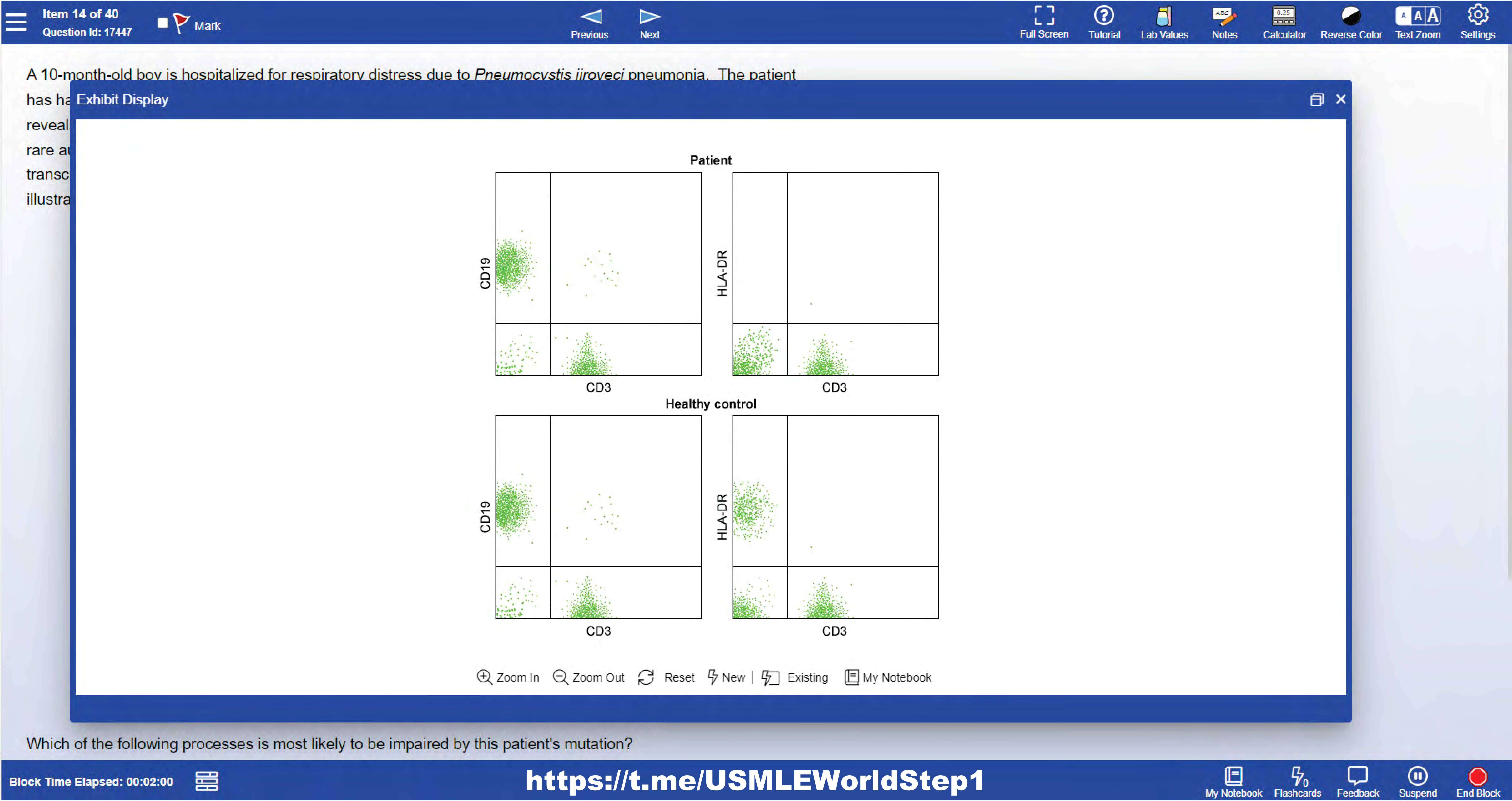
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HLA-DR
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A 10-month-old boy is hospitalized for respiratory distress due to *Pneumocystis jiroveci* pneumonia. The patient
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Which of the following processes is most likely to be impaired by this patient's mutation?

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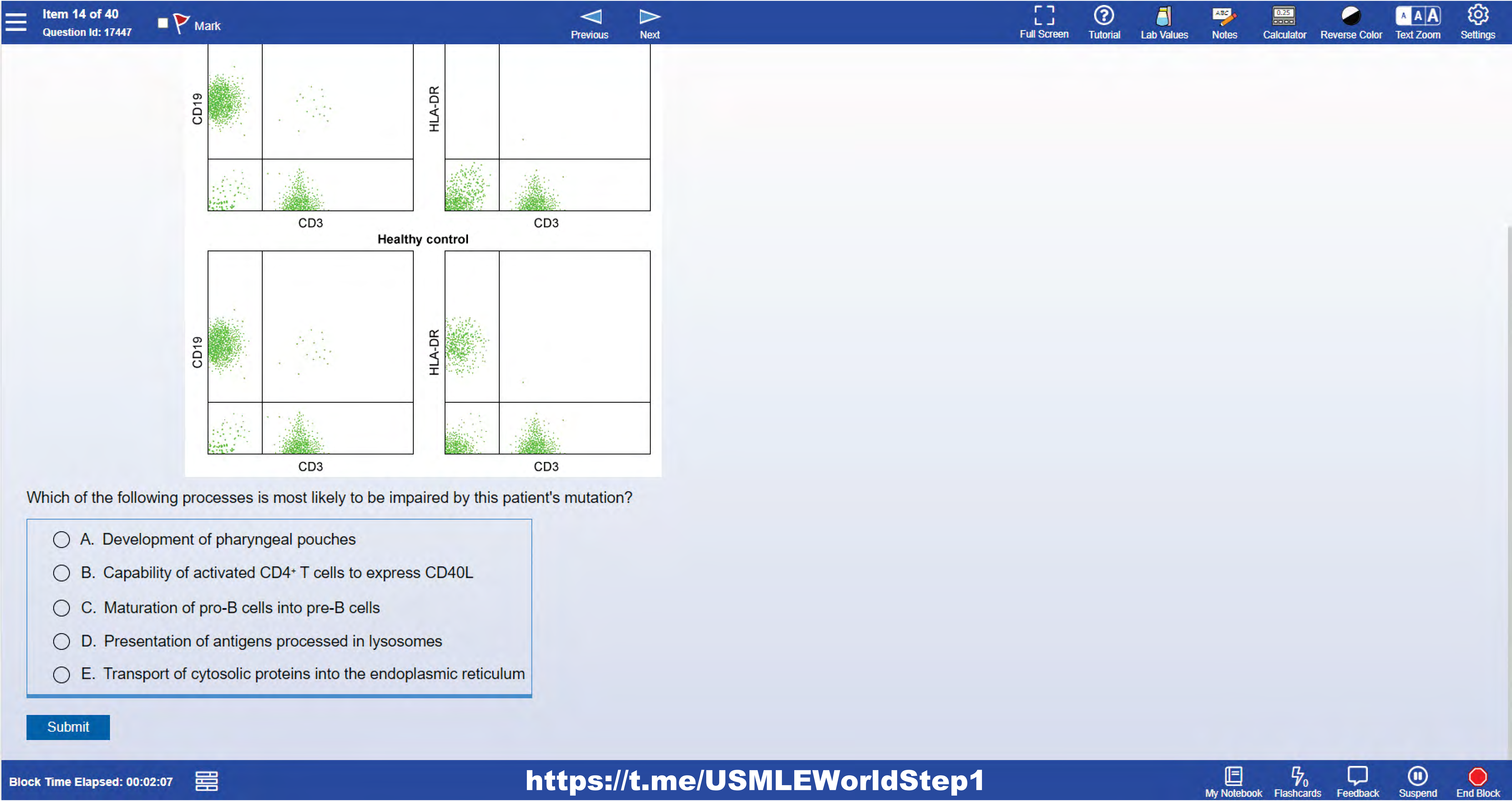
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Item 14 of 40
Question Id: 17447

Which of the following processes is most likely to be impaired by this patient's mutation?

○ A. Development of pharyngeal pouches

○ B. Capability of activated CD4$^+$ T cells to express CD40L

○ C. Maturation of pro-B cells into pre-B cells

○ D. Presentation of antigens processed in lysosomes

○ E. Transport of cytosolic proteins into the endoplasmic reticulum

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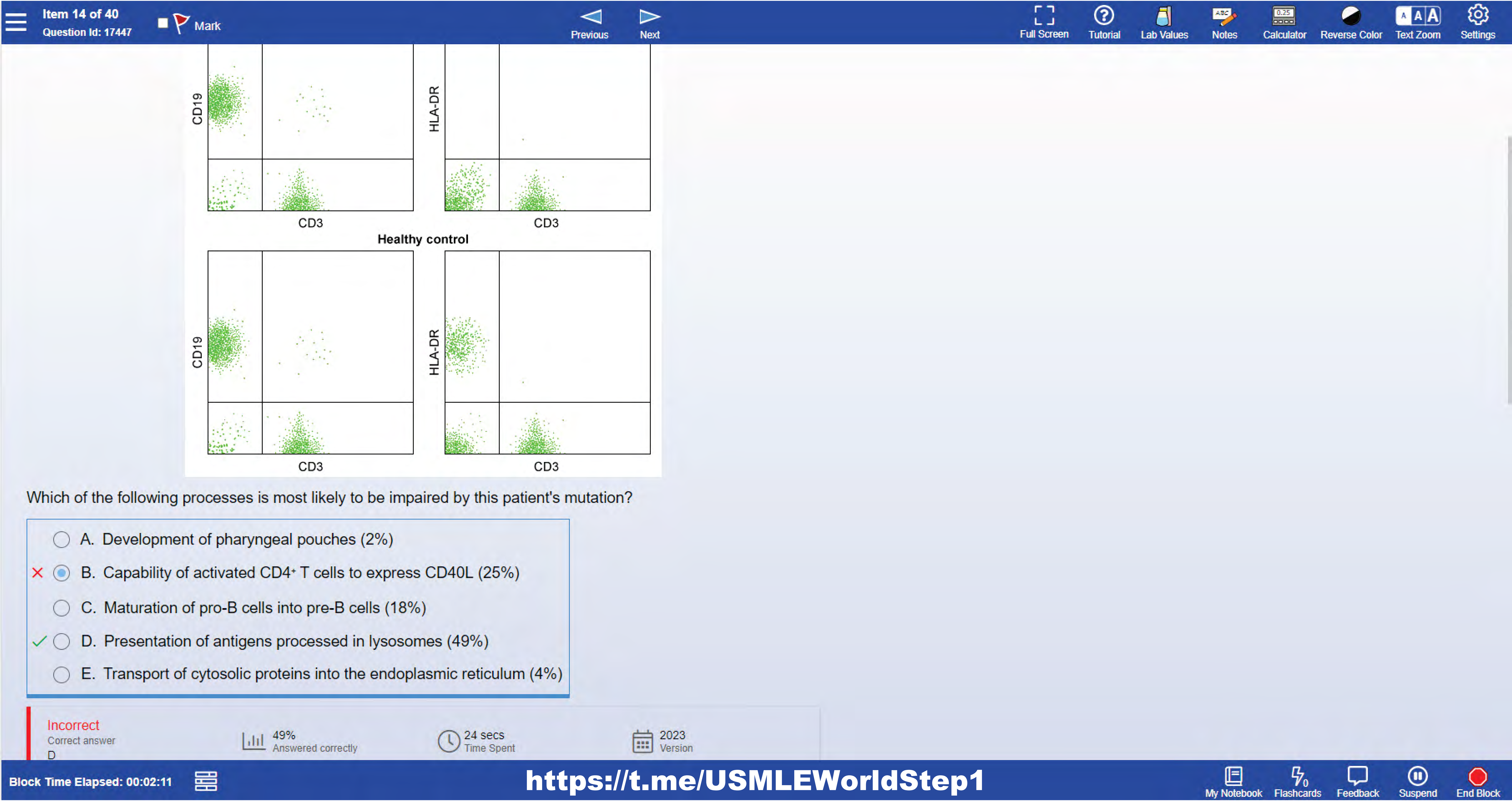
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Which of the following processes is most likely to be impaired by this patient's mutation?

- ○ A. Development of pharyngeal pouches (2%)
- ✗ ● B. Capability of activated CD4$^+$ T cells to express CD40L (25%)
- ○ C. Maturation of pro-B cells into pre-B cells (18%)
- ✓ ○ D. Presentation of antigens processed in lysosomes (49%)
- ○ E. Transport of cytosolic proteins into the endoplasmic reticulum (4%)

Incorrect
Correct answer
D

49%
Answered correctly

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Explanation

This patient's flow cytometry shows normal numbers of CD3$^+$ cells (reflecting circulating T cells) and CD19$^+$ cells (reflecting circulating B cells). However, an absence of HLA-DR$^+$ cells indicates defective expression of major histocompatibility complex (MHC) class II molecules. The human leukocyte antigen (HLA) genes encode MHC molecules expressed on the cell surface for antigen presentation. There are 6 major HLA loci:

- *HLA-DP*, *HLA-DQ*, and ***HLA-DR*** genes encode **MHC class II** molecules, which are expressed on **antigen-presenting cells** (eg, B cells, macrophages) after an extracellular antigen has been loaded onto the MHC class II molecule in an acidified **lysosome**.
- *HLA-A*, *HLA-B*, and *HLA-C* genes encode MHC class I molecules, which are expressed on nucleated cells after a cytosolic antigen has been transported into the endoplasmic reticulum and loaded onto the MHC class I molecule **(Choice E)**.

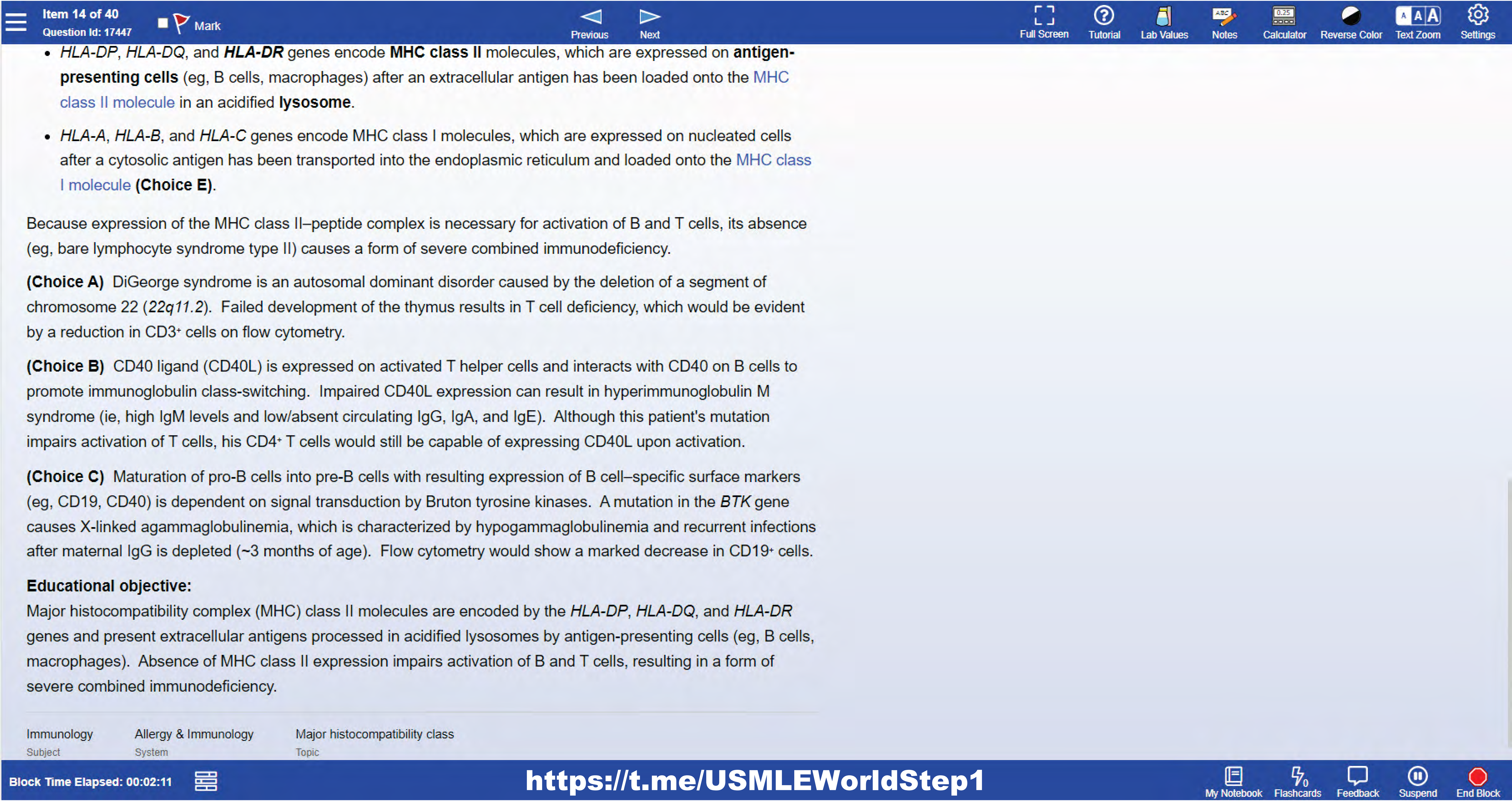
Because expression of the MHC class II–peptide complex is necessary for activation of B and T cells, its absence (eg, bare lymphocyte syndrome type II) causes a form of severe combined immunodeficiency.

(Choice A) DiGeorge syndrome is an autosomal dominant disorder caused by the deletion of a segment of chromosome 22 (*22q11.2*). Failed development of the thymus results in T cell deficiency, which would be evident by a reduction in CD3$^+$ cells on flow cytometry.

(Choice B) CD40 ligand (CD40L) is expressed on activated T helper cells and interacts with CD40 on B cells to promote immunoglobulin class-switching. Impaired CD40L expression can result in hyperimmunoglobulin M syndrome (ie, high IgM levels and low/absent circulating IgG, IgA, and IgE). Although this patient's mutation impairs activation of T cells, his CD4$^+$ T cells would still be capable of expressing CD40L upon activation.

(Choice C) Maturation of pro-B cells into pre-B cells with resulting expression of B cell–specific surface markers (eg, CD19, CD40) is dependent on signal transduction by Bruton tyrosine kinases. A mutation in the *BTK* gene causes X-linked agammaglobulinemia, which is characterized by hypogammaglobulinemia and recurrent infections after maternal IgG is depleted (~3 months of age). Flow cytometry would show a marked decrease in CD19$^+$ cells.

Educational objective:



- *HLA-DP*, *HLA-DQ*, and ***HLA-DR*** genes encode **MHC class II** molecules, which are expressed on **antigen-presenting cells** (eg, B cells, macrophages) after an extracellular antigen has been loaded onto the MHC class II molecule in an acidified **lysosome**.
- *HLA-A*, *HLA-B*, and *HLA-C* genes encode MHC class I molecules, which are expressed on nucleated cells after a cytosolic antigen has been transported into the endoplasmic reticulum and loaded onto the MHC class I molecule **(Choice E)**.

Because expression of the MHC class II–peptide complex is necessary for activation of B and T cells, its absence (eg, bare lymphocyte syndrome type II) causes a form of severe combined immunodeficiency.

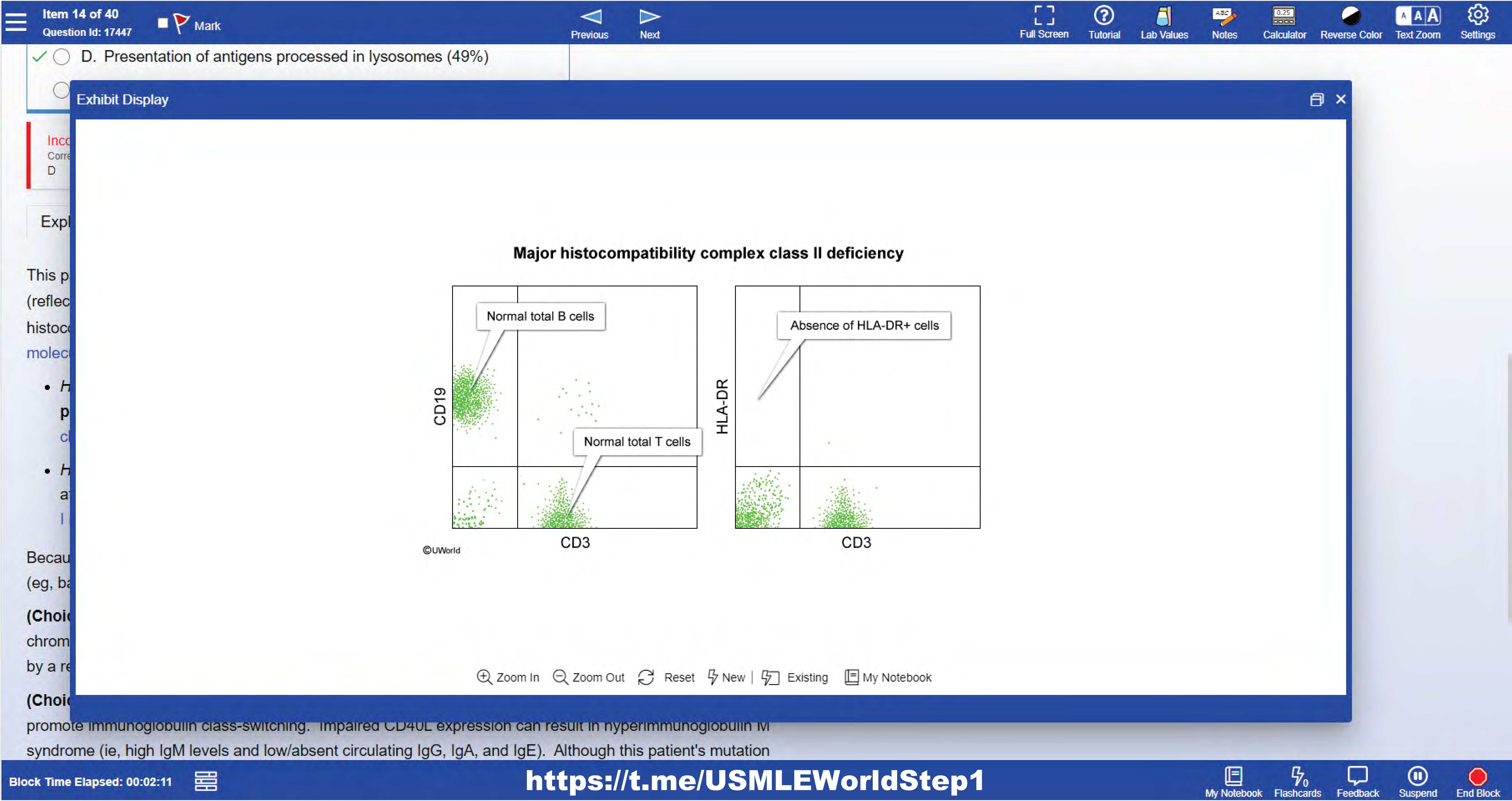
(Choice A) DiGeorge syndrome is an autosomal dominant disorder caused by the deletion of a segment of chromosome 22 (*22q11.2*). Failed development of the thymus results in T cell deficiency, which would be evident by a reduction in CD3$^+$ cells on flow cytometry.

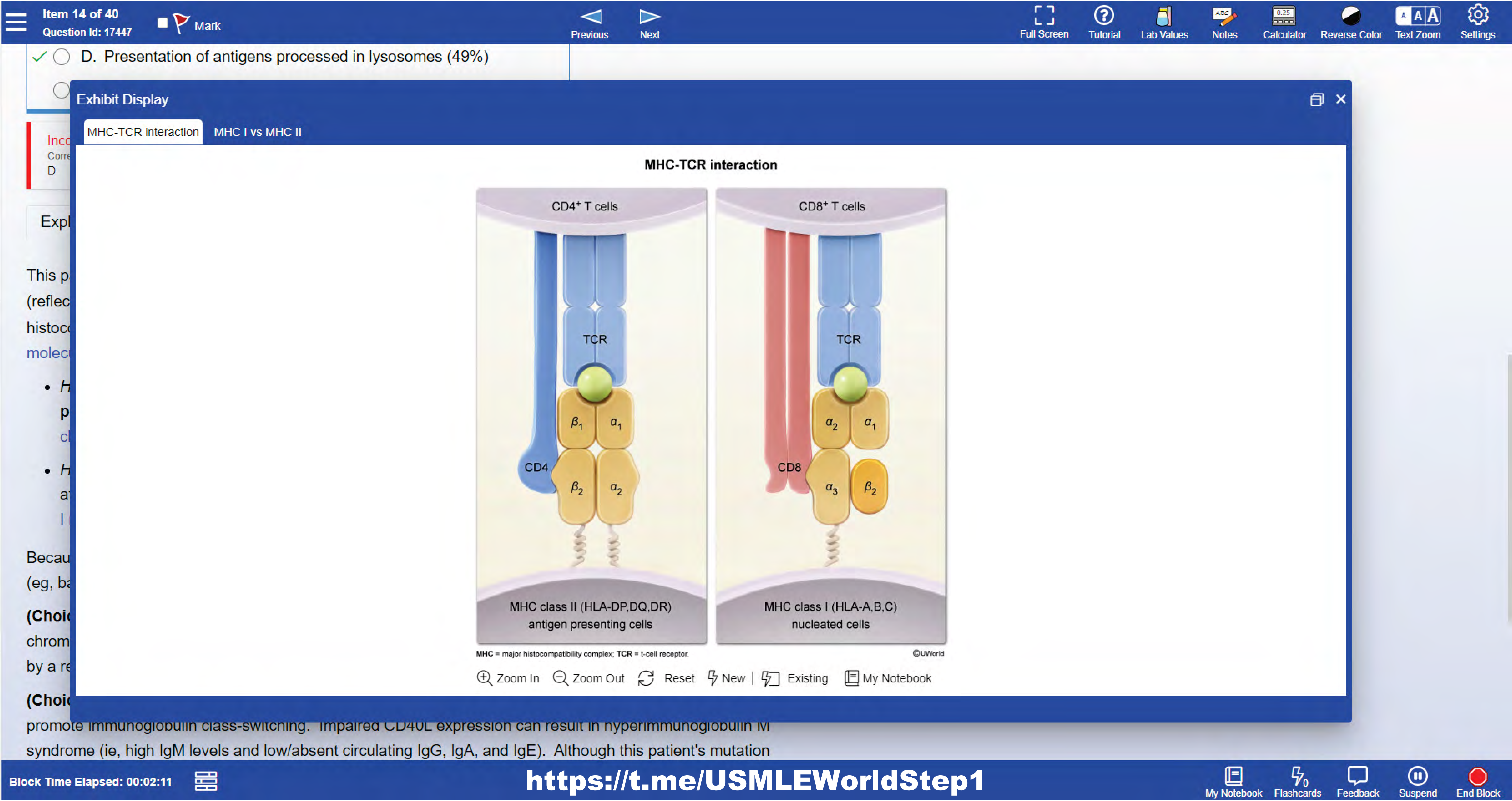
(Choice B) CD40 ligand (CD40L) is expressed on activated T helper cells and interacts with CD40 on B cells to promote immunoglobulin class-switching. Impaired CD40L expression can result in hyperimmunoglobulin M syndrome (ie, high IgM levels and low/absent circulating IgG, IgA, and IgE). Although this patient's mutation impairs activation of T cells, his CD4$^+$ T cells would still be capable of expressing CD40L upon activation.

(Choice C) Maturation of pro-B cells into pre-B cells with resulting expression of B cell–specific surface markers (eg, CD19, CD40) is dependent on signal transduction by Bruton tyrosine kinases. A mutation in the *BTK* gene causes X-linked agammaglobulinemia, which is characterized by hypogammaglobulinemia and recurrent infections after maternal IgG is depleted (~3 months of age). Flow cytometry would show a marked decrease in CD19$^+$ cells.

Educational objective:
Major histocompatibility complex (MHC) class II molecules are encoded by the *HLA-DP*, *HLA-DQ*, and *HLA-DR* genes and present extracellular antigens processed in acidified lysosomes by antigen-presenting cells (eg, B cells, macrophages). Absence of MHC class II expression impairs activation of B and T cells, resulting in a form of severe combined immunodeficiency.

Immunology	Allergy & Immunology	Major histocompatibility class
Subject	System	Topic

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✓ ○ D. Presentation of antigens processed in lysosomes (49%)

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promote immunoglobulin class-switching. Impaired CD40L expression can result in hyperimmunoglobulin M syndrome (ie, high IgM levels and low/absent circulating IgG, IgA, and IgE). Although this patient's mutation

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MHC-TCR interaction | MHC I vs MHC II

MHC-TCR interaction

CD4⁺ T cells
TCR
β1
α1
CD4
β2
α2
MHC class II (HLA-DP,DQ,DR)
antigen presenting cells
CD8⁺ T cells
TCR
α2
α1
CD8
α3
β2
MHC class I (HLA-A,B,C)
nucleated cells

MHC = major histocompatibility complex; **TCR** = t-cell receptor.

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✓ ○ D. Presentation of antigens processed in lysosomes (49%)

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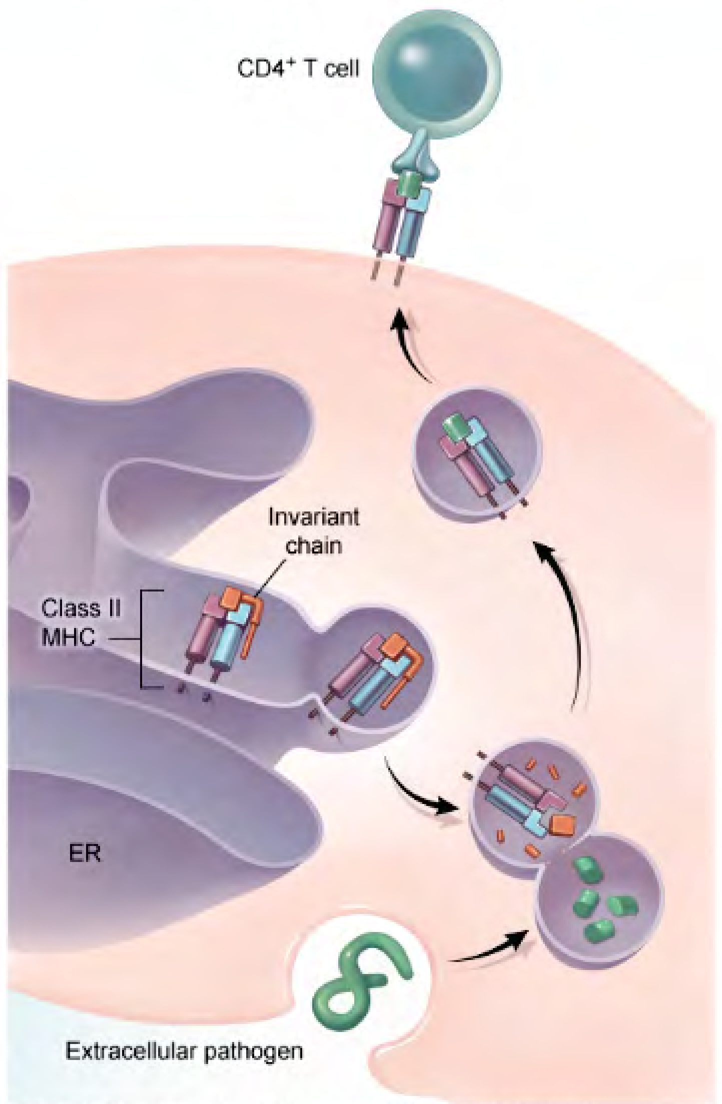
Class II MHC pathway


CD4⁺ T cell
Invariant chain
Class II MHC
ER
Extracellular pathogen

ER = endoplasmic reticulum; MHC = major histocompatibility complex. ©UWorld

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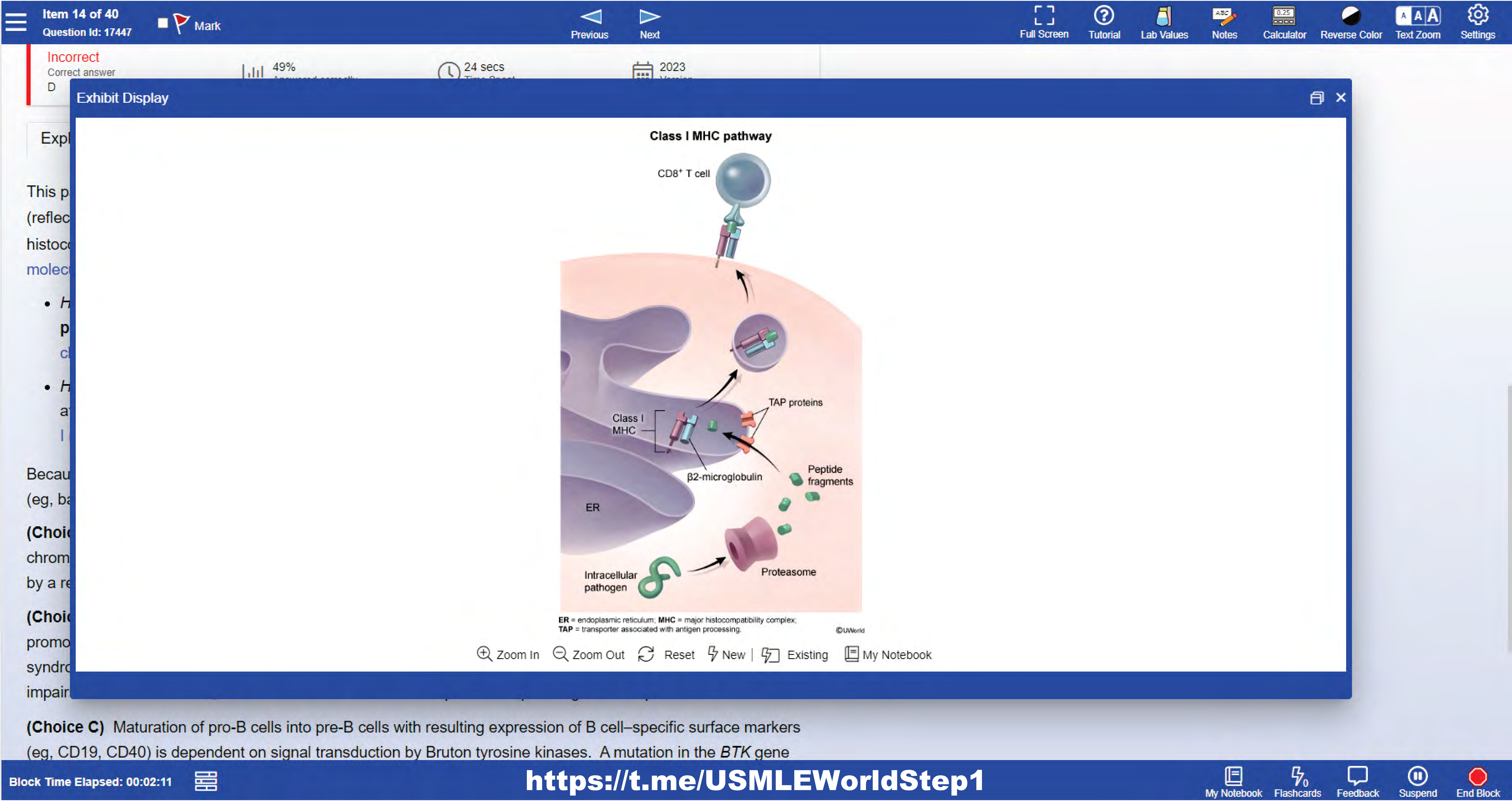
(Choice B) CD40 ligand (CD40L) is expressed on activated T helper cells and interacts with CD40 on B cells to promote immunoglobulin class-switching. Impaired CD40L expression can result in hyperimmunoglobulin M syndrome (ie, high IgM levels and low/absent circulating IgG, IgA, and IgE). Although this patient's mutation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Class I MHC pathway

CD8⁺ T cell
Class I MHC
TAP proteins
β2-microglobulin
Peptide fragments
ER
Intracellular pathogen
Proteasome

ER = endoplasmic reticulum; **MHC** = major histocompatibility complex; **TAP** = transporter associated with antigen processing.

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(Choice C) Maturation of pro-B cells into pre-B cells with resulting expression of B cell–specific surface markers (eg, CD19, CD40) is dependent on signal transduction by Bruton tyrosine kinases. A mutation in the *BTK* gene

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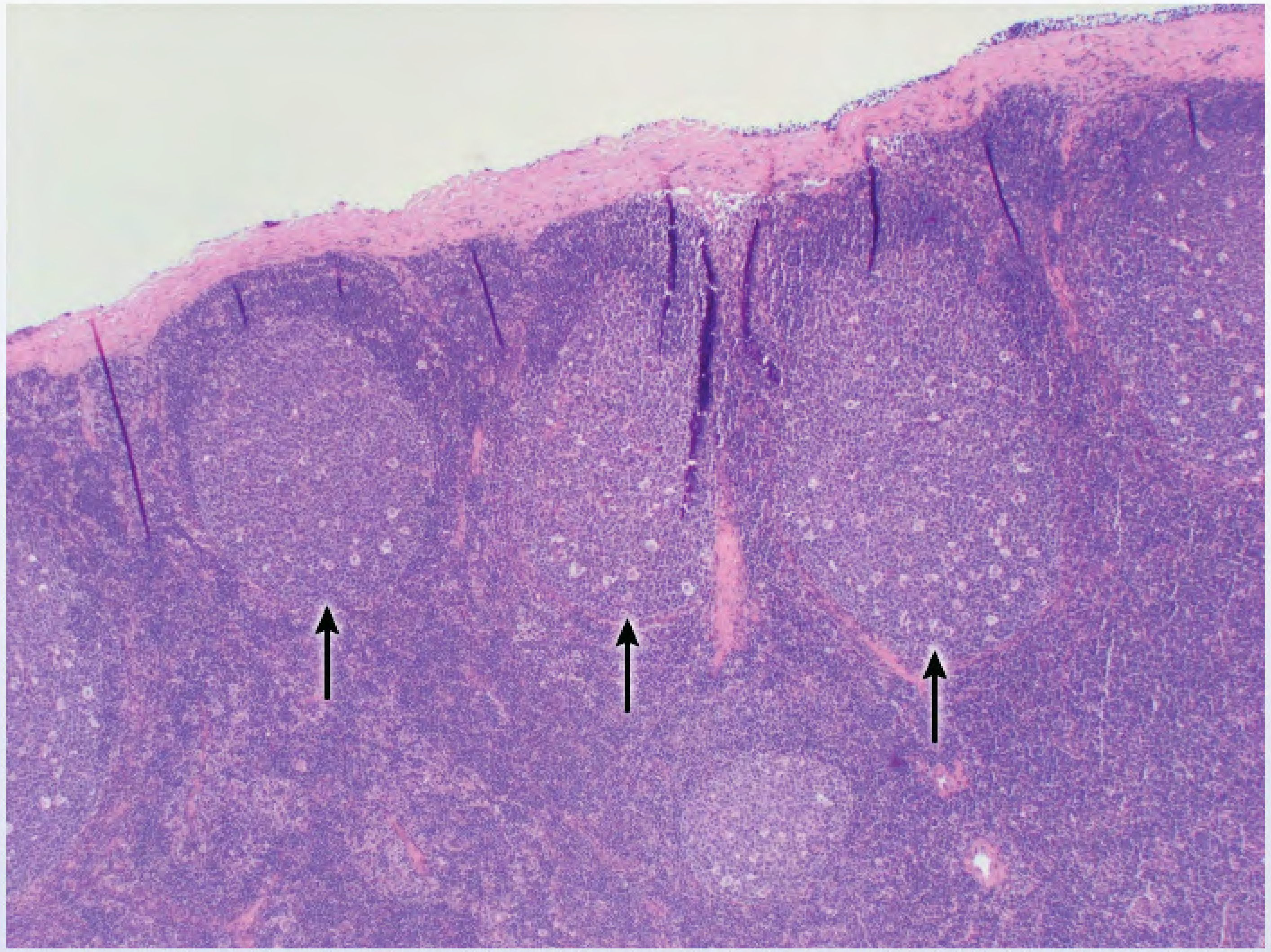
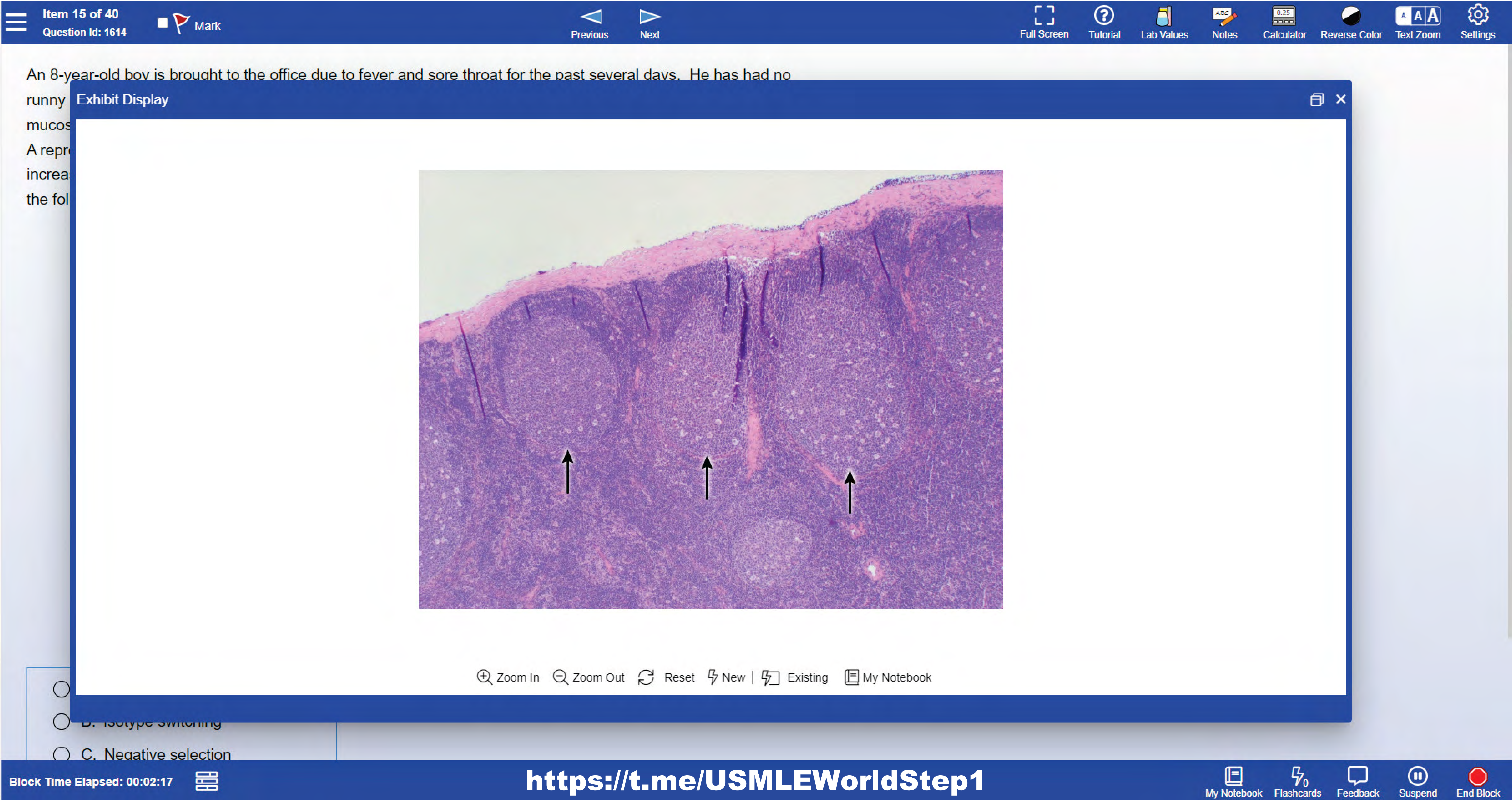
An 8-year-old boy is brought to the office due to fever and sore throat for the past several days. He has had no runny nose or cough. Temperature is 38.4 C (101.1 F). Physical examination shows erythematous pharyngeal mucosa with enlarged tonsils covered by exudates. There are enlarged and tender anterior cervical lymph nodes. A representative image of one of the enlarged nodes is shown below; the structures indicated by the arrows are increased in size and number. The predominant cell type within these regions is most likely undergoing which of the following processes?



○ A. Development of central tolerance

○ B. Isotype switching

○ C. Negative selection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An 8-year-old boy is brought to the office due to fever and sore throat for the past several days. He has had no

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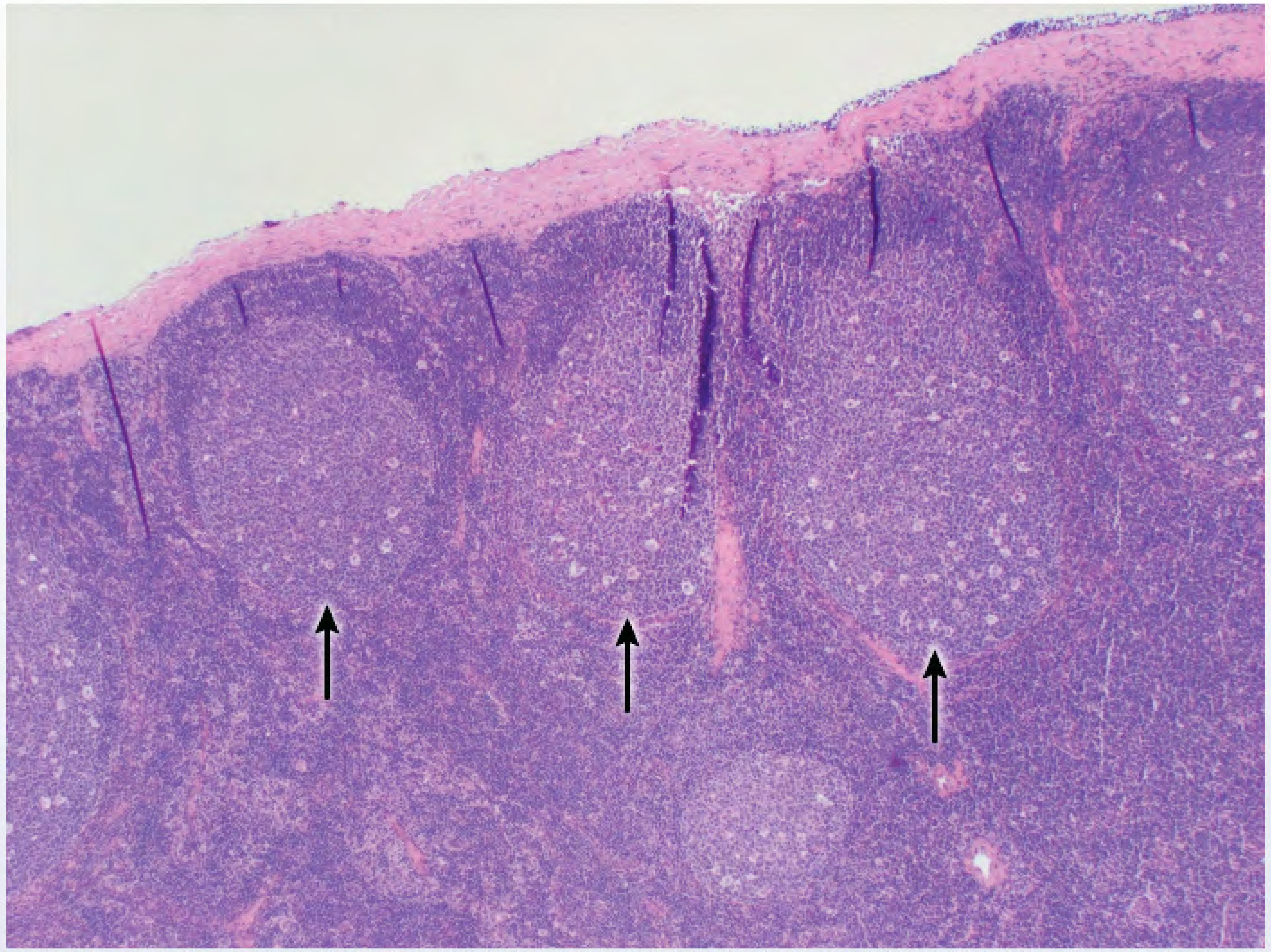
○ B. Isotype switching

○ C. Negative selection

the following processes?



○ A. Development of central tolerance
○ B. Isotype switching
○ C. Negative selection
○ D. V(D)J recombination
○ E. VJ recombination

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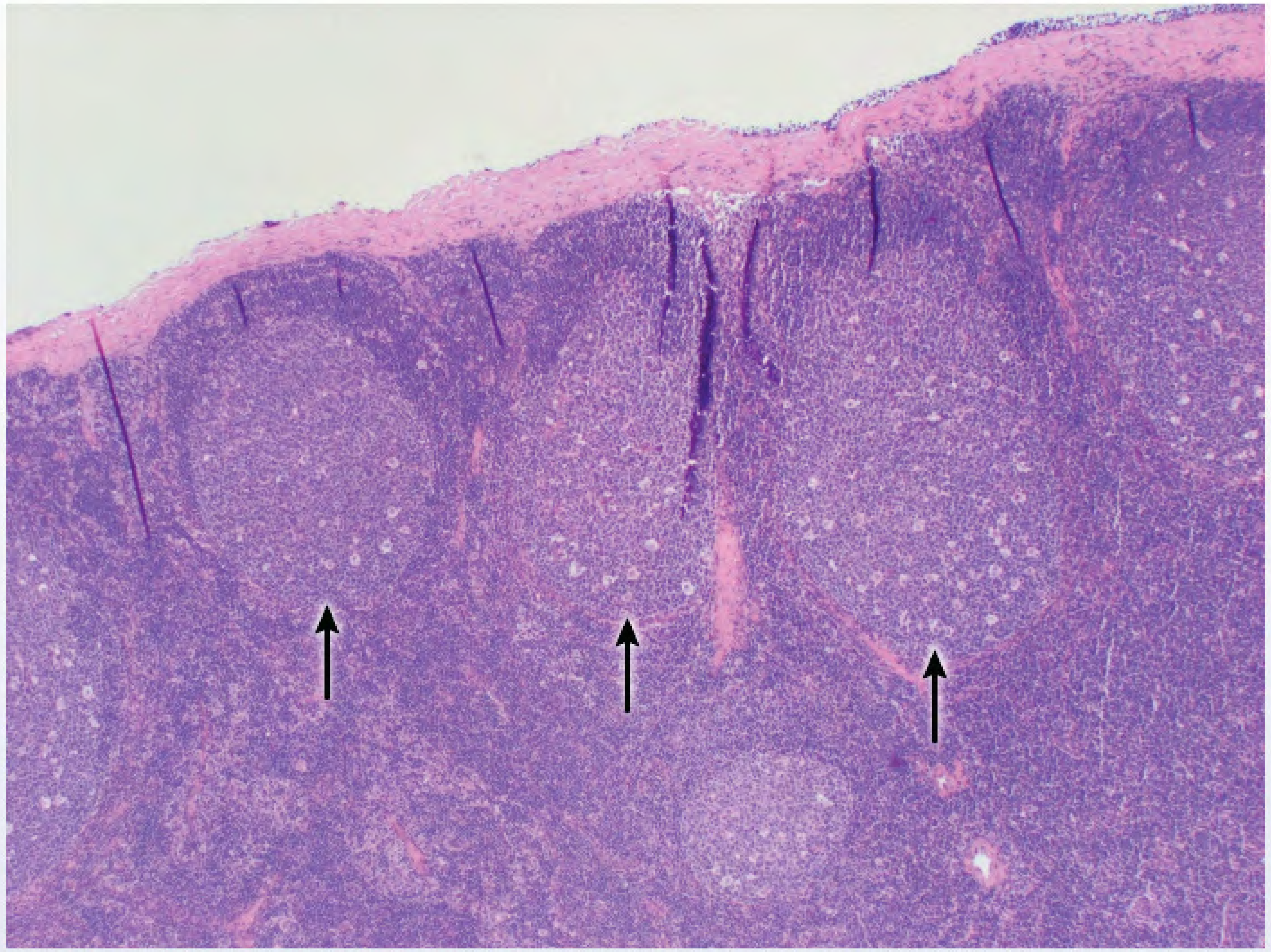
the following processes?



- ○ A. Development of central tolerance (4%)
- ✓ ● B. Isotype switching (57%)
- ○ C. Negative selection (12%)
- ○ D. V(D)J recombination (21%)
- ○ E. VJ recombination (3%)

Correct

57% Answered correctly

13 secs Time Spent

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Explanation

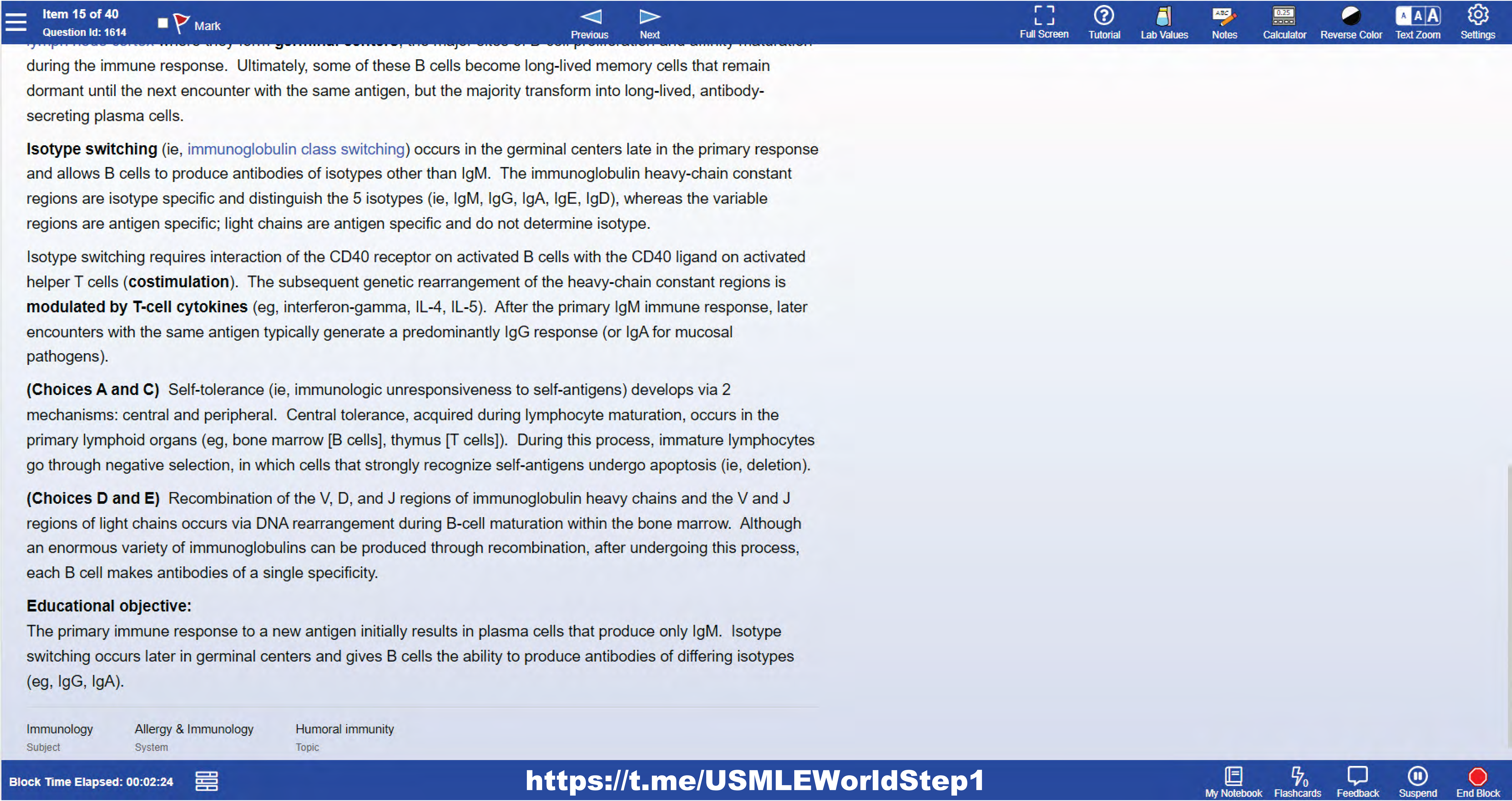
After development in the bone marrow, mature B cells migrate to peripheral lymphoid organs (eg, lymph nodes), where they are exposed to antigens. On first exposure to a new antigen, naïve **B cells** become activated and undergo clonal expansion. Some differentiate into short-lived plasma cells that release antigen-specific IgM through a T-cell–independent process. However, most activated B cells migrate to lymphoid follicles located in the lymph node cortex where they form **germinal centers**, the major sites of B-cell proliferation and affinity maturation during the immune response. Ultimately, some of these B cells become long-lived memory cells that remain dormant until the next encounter with the same antigen, but the majority transform into long-lived, antibody-secreting plasma cells.

Isotype switching (ie, immunoglobulin class switching) occurs in the germinal centers late in the primary response and allows B cells to produce antibodies of isotypes other than IgM. The immunoglobulin heavy-chain constant regions are isotype specific and distinguish the 5 isotypes (ie, IgM, IgG, IgA, IgE, IgD), whereas the variable regions are antigen specific; light chains are antigen specific and do not determine isotype.

Isotype switching requires interaction of the CD40 receptor on activated B cells with the CD40 ligand on activated helper T cells (**costimulation**). The subsequent genetic rearrangement of the heavy-chain constant regions is **modulated by T-cell cytokines** (eg, interferon-gamma, IL-4, IL-5). After the primary IgM immune response, later encounters with the same antigen typically generate a predominantly IgG response (or IgA for mucosal pathogens).

(Choices A and C) Self-tolerance (ie, immunologic unresponsiveness to self-antigens) develops via 2 mechanisms: central and peripheral. Central tolerance, acquired during lymphocyte maturation, occurs in the primary lymphoid organs (eg, bone marrow [B cells], thymus [T cells]). During this process, immature lymphocytes go through negative selection, in which cells that strongly recognize self-antigens undergo apoptosis (ie, deletion).

(Choices D and E) Recombination of the V, D, and J regions of immunoglobulin heavy chains and the V and J regions of light chains occurs via DNA rearrangement during B-cell maturation within the bone marrow. Although an enormous variety of immunoglobulins can be produced through recombination, after undergoing this process, each B cell makes antibodies of a single specificity.



during the immune response. Ultimately, some of these B cells become long-lived memory cells that remain dormant until the next encounter with the same antigen, but the majority transform into long-lived, antibody-secreting plasma cells.

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Isotype switching requires interaction of the CD40 receptor on activated B cells with the CD40 ligand on activated helper T cells (**costimulation**). The subsequent genetic rearrangement of the heavy-chain constant regions is **modulated by T-cell cytokines** (eg, interferon-gamma, IL-4, IL-5). After the primary IgM immune response, later encounters with the same antigen typically generate a predominantly IgG response (or IgA for mucosal pathogens).

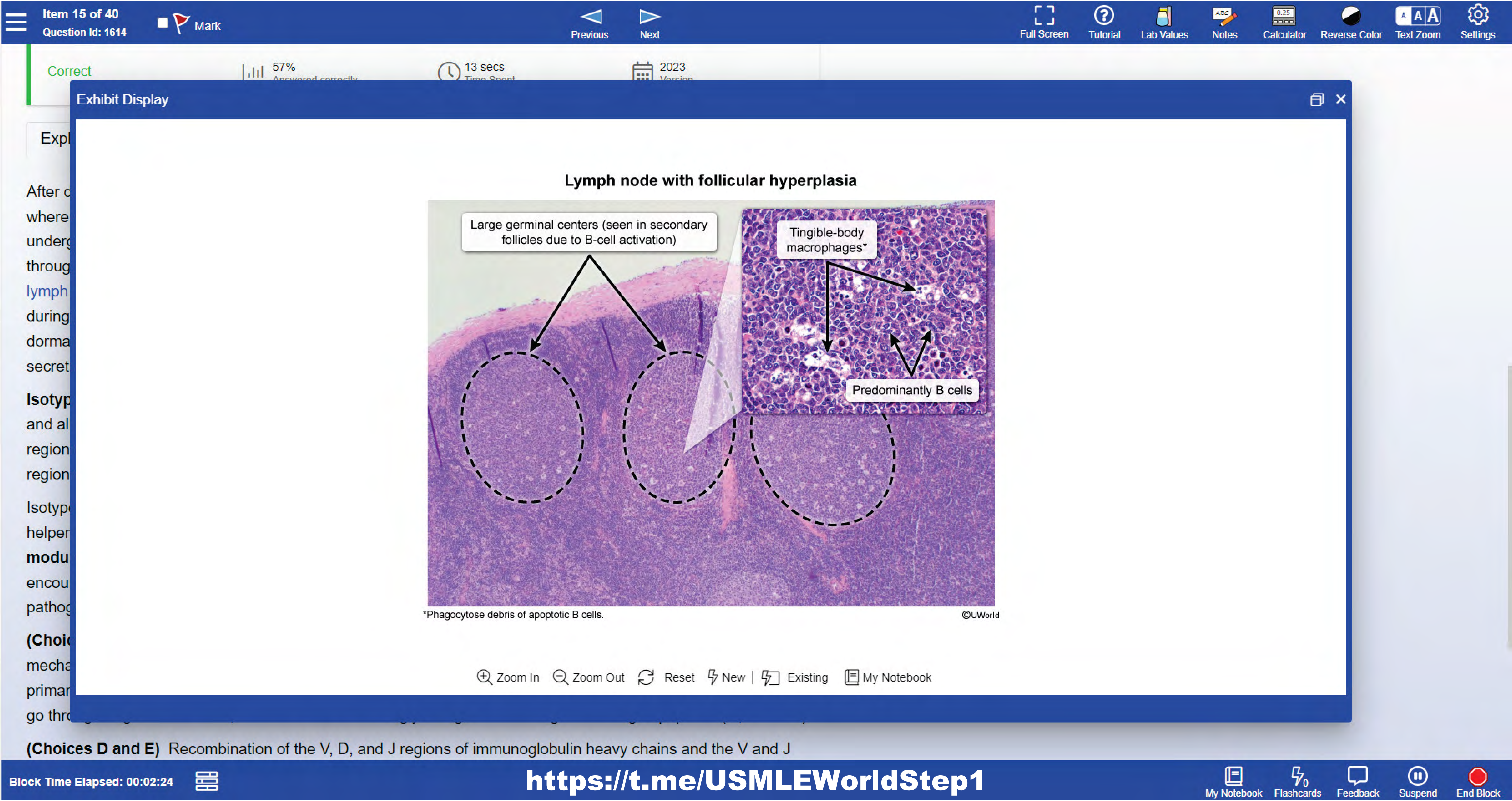
(Choices A and C) Self-tolerance (ie, immunologic unresponsiveness to self-antigens) develops via 2 mechanisms: central and peripheral. Central tolerance, acquired during lymphocyte maturation, occurs in the primary lymphoid organs (eg, bone marrow [B cells], thymus [T cells]). During this process, immature lymphocytes go through negative selection, in which cells that strongly recognize self-antigens undergo apoptosis (ie, deletion).

(Choices D and E) Recombination of the V, D, and J regions of immunoglobulin heavy chains and the V and J regions of light chains occurs via DNA rearrangement during B-cell maturation within the bone marrow. Although an enormous variety of immunoglobulins can be produced through recombination, after undergoing this process, each B cell makes antibodies of a single specificity.

Educational objective:

The primary immune response to a new antigen initially results in plasma cells that produce only IgM. Isotype switching occurs later in germinal centers and gives B cells the ability to produce antibodies of differing isotypes (eg, IgG, IgA).

Immunology	Allergy & Immunology	Humoral immunity
Subject	System	Topic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Lymph node with follicular hyperplasia

Large germinal centers (seen in secondary follicles due to B-cell activation)
Tingible-body macrophages*
Predominantly B cells

*Phagocytose debris of apoptotic B cells.

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(Choices D and E) Recombination of the V, D, and J regions of immunoglobulin heavy chains and the V and J

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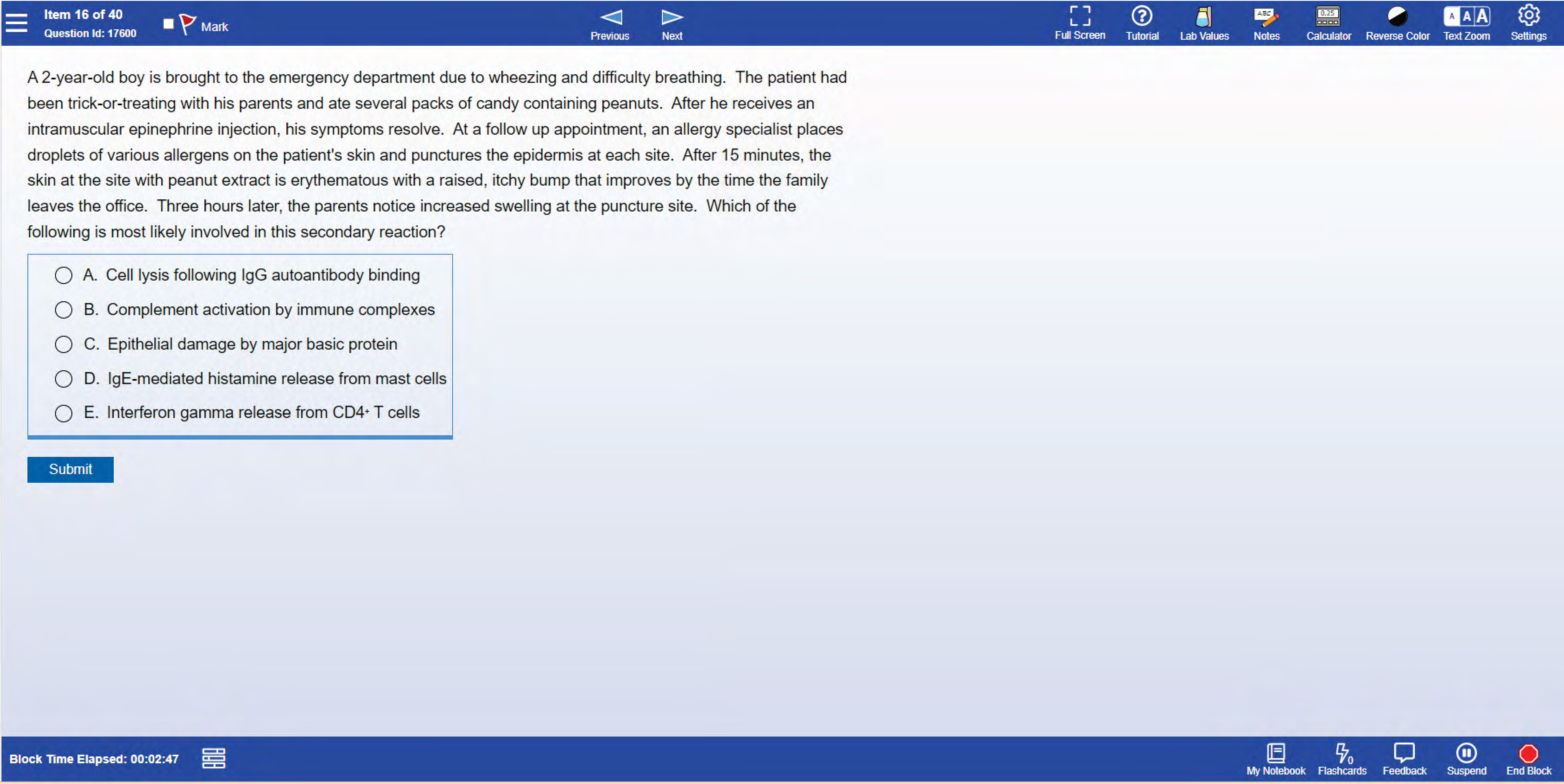
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Question Id: 17600

A 2-year-old boy is brought to the emergency department due to wheezing and difficulty breathing. The patient had been trick-or-treating with his parents and ate several packs of candy containing peanuts. After he receives an intramuscular epinephrine injection, his symptoms resolve. At a follow up appointment, an allergy specialist places droplets of various allergens on the patient's skin and punctures the epidermis at each site. After 15 minutes, the skin at the site with peanut extract is erythematous with a raised, itchy bump that improves by the time the family leaves the office. Three hours later, the parents notice increased swelling at the puncture site. Which of the following is most likely involved in this secondary reaction?

○ A. Cell lysis following IgG autoantibody binding
○ B. Complement activation by immune complexes
○ C. Epithelial damage by major basic protein
○ D. IgE-mediated histamine release from mast cells
○ E. Interferon gamma release from $CD4^+$ T cells

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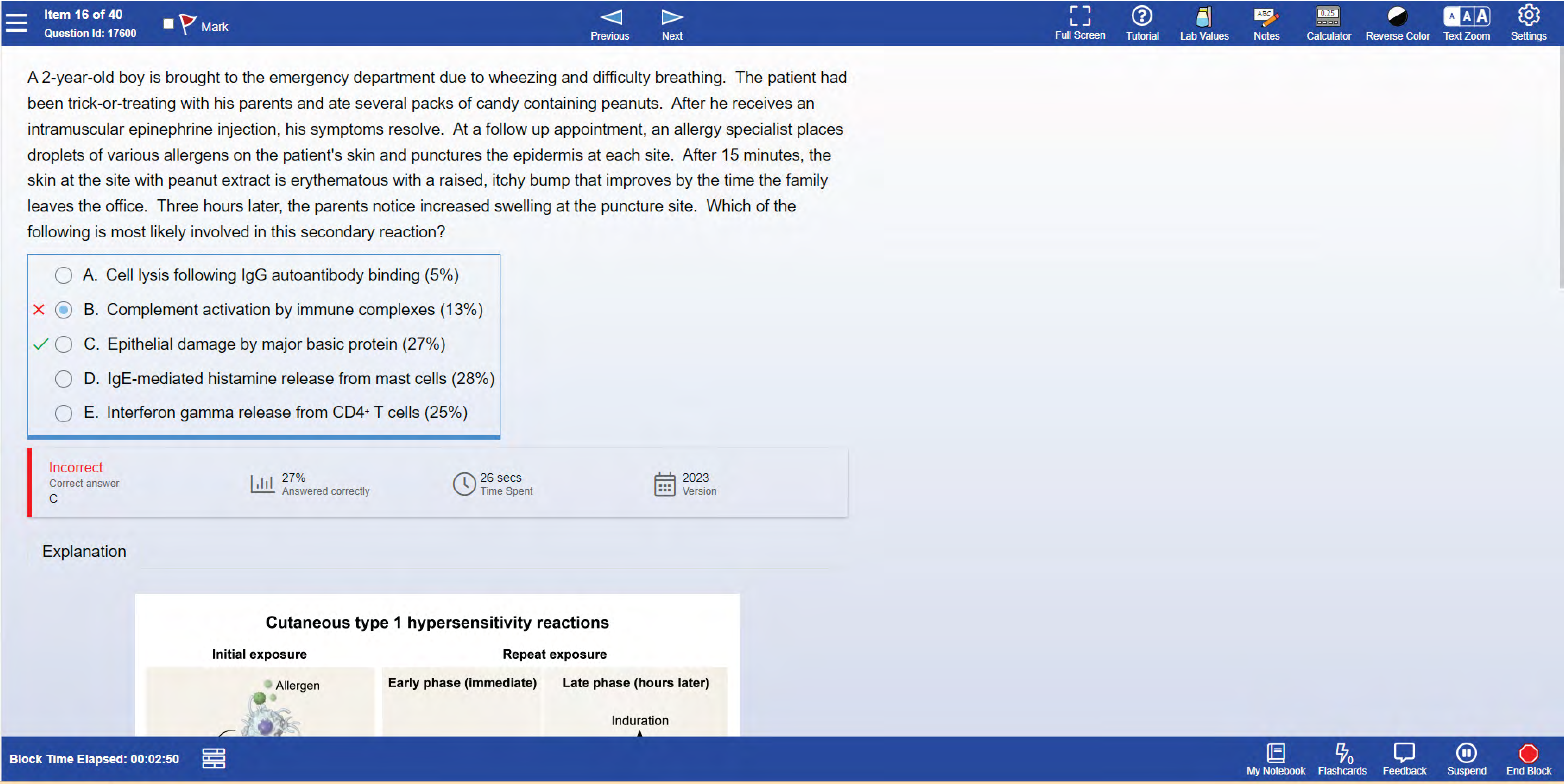
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- ○ A. Cell lysis following IgG autoantibody binding (5%)
- ✗ ● B. Complement activation by immune complexes (13%)
- ✓ ○ C. Epithelial damage by major basic protein (27%)
- ○ D. IgE-mediated histamine release from mast cells (28%)
- ○ E. Interferon gamma release from $CD4^+$ T cells (25%)

Incorrect
Correct answer
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27%
Answered correctly

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Explanation

Cutaneous type 1 hypersensitivity reactions

Initial exposure
Repeat exposure
Allergen
Early phase (immediate)
Late phase (hours later)
Induration

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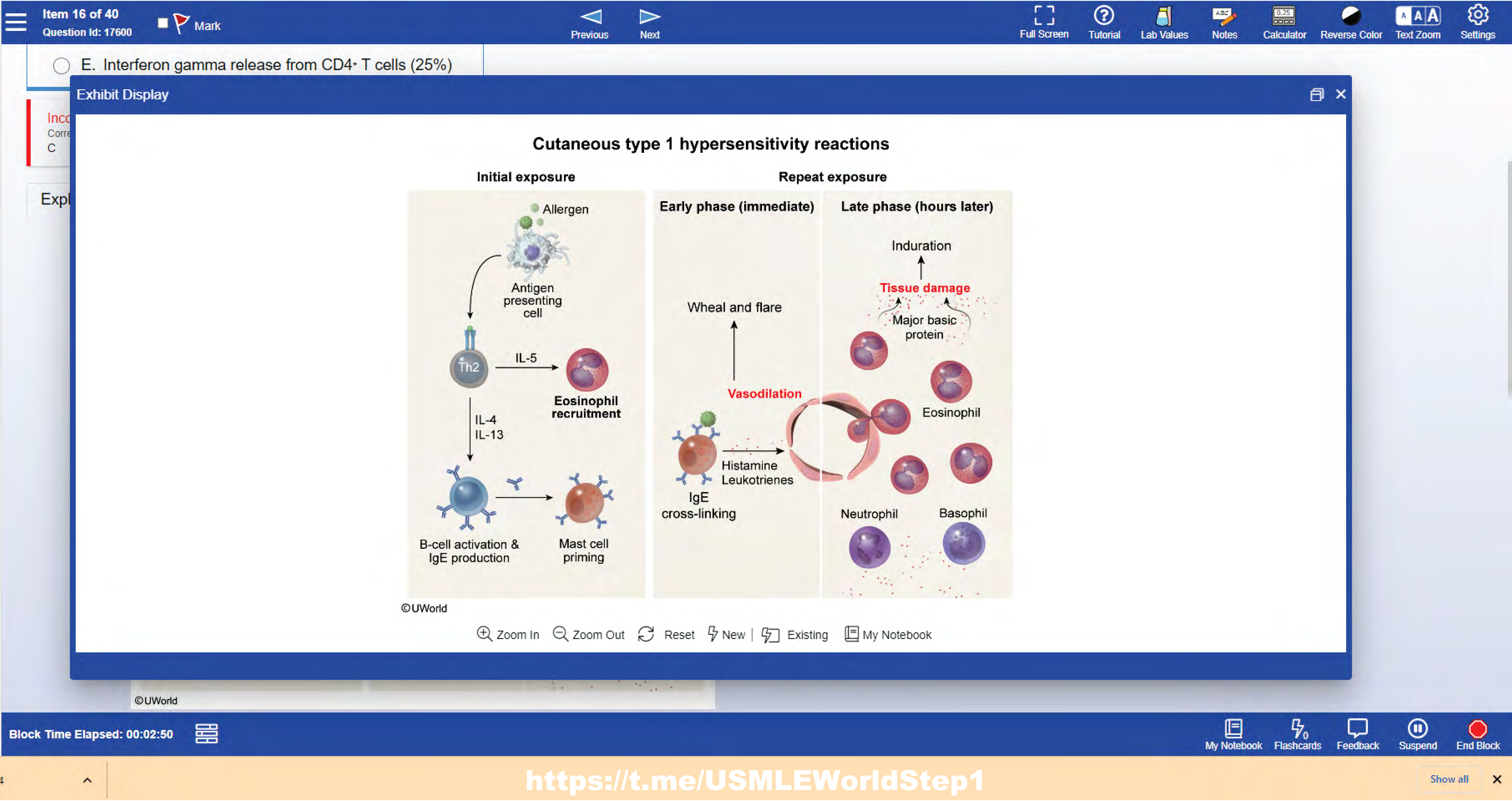

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○ E. Interferon gamma release from CD4+ T cells (25%)

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Cutaneous type 1 hypersensitivity reactions

Initial exposure
Repeat exposure
Early phase (immediate)
Late phase (hours later)
Allergen
Antigen presenting cell
Th2
IL-5
Eosinophil recruitment
IL-4
IL-13
B-cell activation & IgE production
Mast cell priming
Wheal and flare
Vasodilation
IgE cross-linking
Histamine
Leukotrienes
Induration
Tissue damage
Major basic protein
Eosinophil
Neutrophil
Basophil

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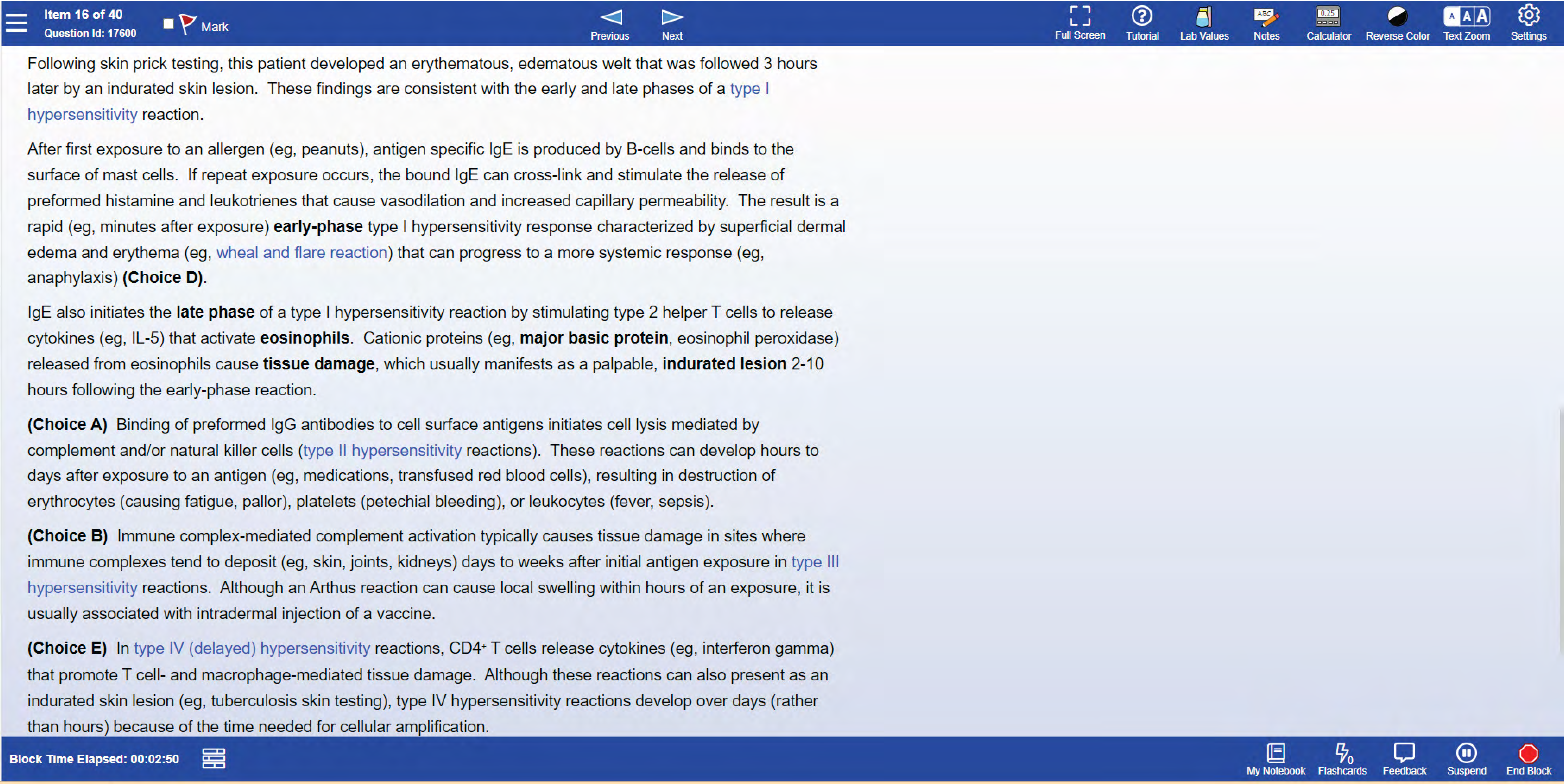


Following skin prick testing, this patient developed an erythematous, edematous welt that was followed 3 hours later by an indurated skin lesion. These findings are consistent with the early and late phases of a type I hypersensitivity reaction.

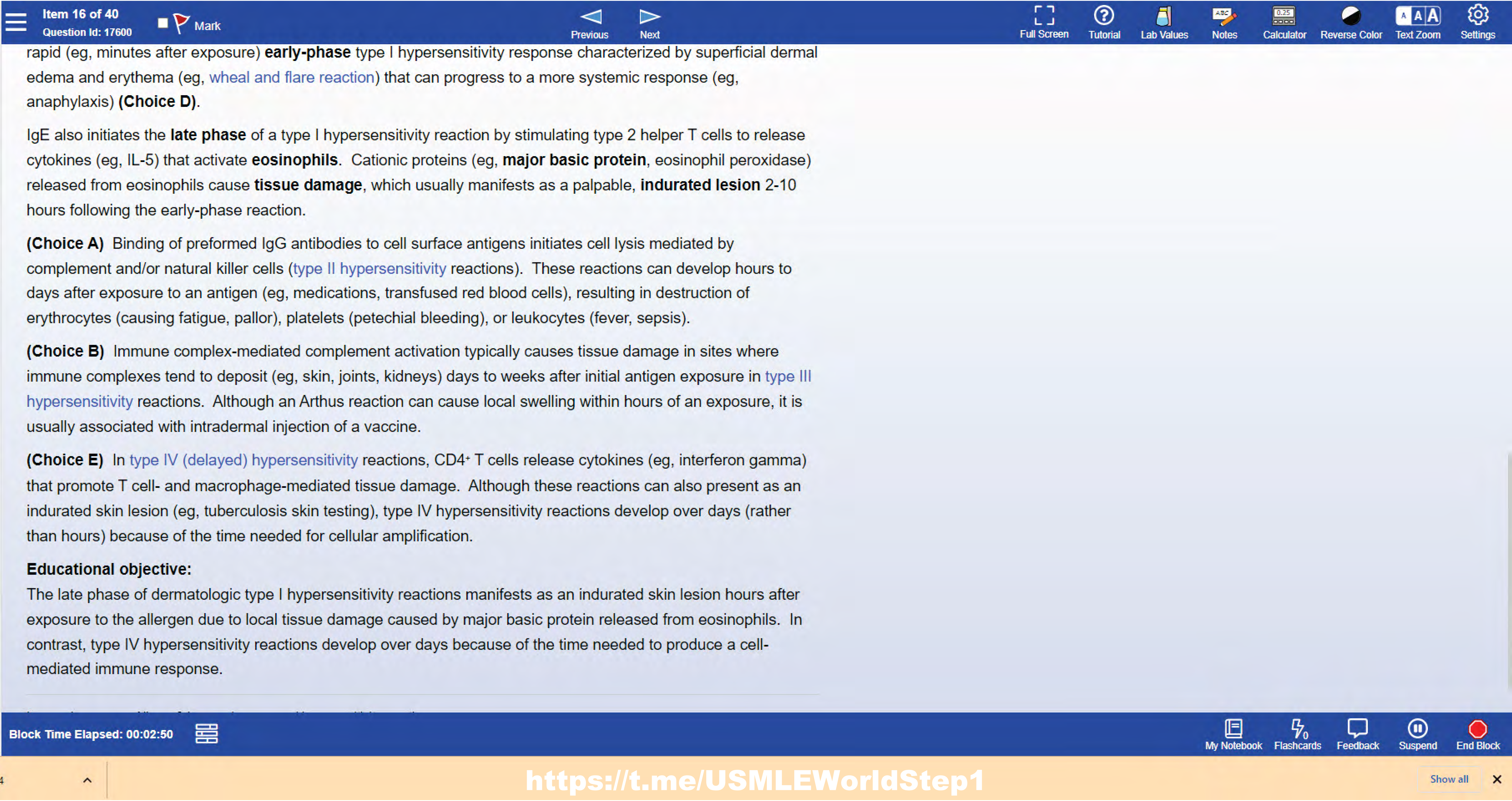
After first exposure to an allergen (eg, peanuts), antigen specific IgE is produced by B-cells and binds to the surface of mast cells. If repeat exposure occurs, the bound IgE can cross-link and stimulate the release of preformed histamine and leukotrienes that cause vasodilation and increased capillary permeability. The result is a rapid (eg, minutes after exposure) **early-phase** type I hypersensitivity response characterized by superficial dermal edema and erythema (eg, wheal and flare reaction) that can progress to a more systemic response (eg, anaphylaxis) **(Choice D)**.

IgE also initiates the **late phase** of a type I hypersensitivity reaction by stimulating type 2 helper T cells to release cytokines (eg, IL-5) that activate **eosinophils**. Cationic proteins (eg, **major basic protein**, eosinophil peroxidase) released from eosinophils cause **tissue damage**, which usually manifests as a palpable, **indurated lesion** 2-10 hours following the early-phase reaction.

(Choice A) Binding of preformed IgG antibodies to cell surface antigens initiates cell lysis mediated by complement and/or natural killer cells (type II hypersensitivity reactions). These reactions can develop hours to days after exposure to an antigen (eg, medications, transfused red blood cells), resulting in destruction of erythrocytes (causing fatigue, pallor), platelets (petechial bleeding), or leukocytes (fever, sepsis).

(Choice B) Immune complex-mediated complement activation typically causes tissue damage in sites where immune complexes tend to deposit (eg, skin, joints, kidneys) days to weeks after initial antigen exposure in type III hypersensitivity reactions. Although an Arthus reaction can cause local swelling within hours of an exposure, it is usually associated with intradermal injection of a vaccine.

(Choice E) In type IV (delayed) hypersensitivity reactions, $CD4^+$ T cells release cytokines (eg, interferon gamma) that promote T cell- and macrophage-mediated tissue damage. Although these reactions can also present as an indurated skin lesion (eg, tuberculosis skin testing), type IV hypersensitivity reactions develop over days (rather than hours) because of the time needed for cellular amplification.



rapid (eg, minutes after exposure) **early-phase** type I hypersensitivity response characterized by superficial dermal edema and erythema (eg, wheal and flare reaction) that can progress to a more systemic response (eg, anaphylaxis) **(Choice D)**.

IgE also initiates the **late phase** of a type I hypersensitivity reaction by stimulating type 2 helper T cells to release cytokines (eg, IL-5) that activate **eosinophils**. Cationic proteins (eg, **major basic protein**, eosinophil peroxidase) released from eosinophils cause **tissue damage**, which usually manifests as a palpable, **indurated lesion** 2-10 hours following the early-phase reaction.

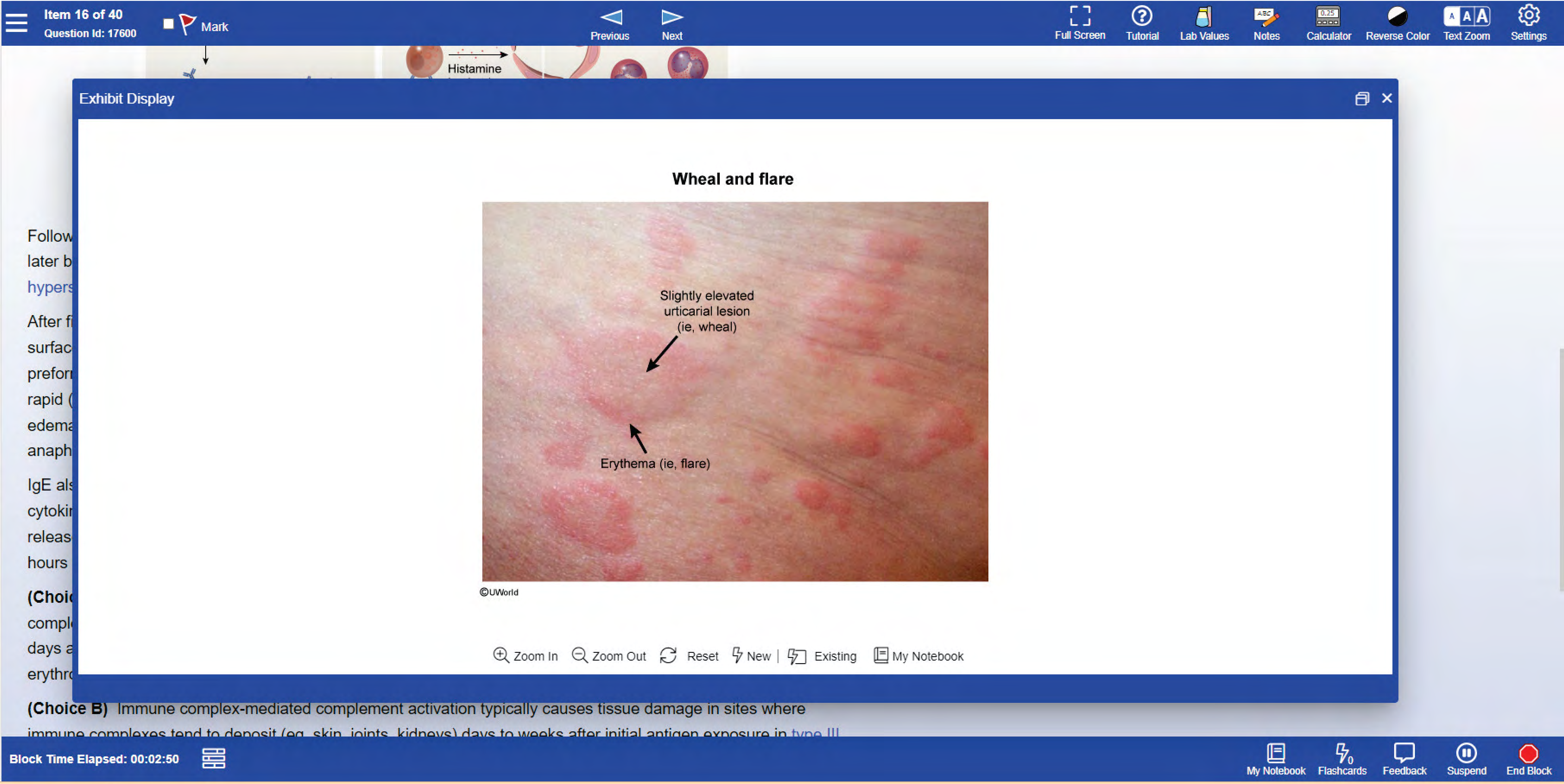
(Choice A) Binding of preformed IgG antibodies to cell surface antigens initiates cell lysis mediated by complement and/or natural killer cells (type II hypersensitivity reactions). These reactions can develop hours to days after exposure to an antigen (eg, medications, transfused red blood cells), resulting in destruction of erythrocytes (causing fatigue, pallor), platelets (petechial bleeding), or leukocytes (fever, sepsis).

(Choice B) Immune complex-mediated complement activation typically causes tissue damage in sites where immune complexes tend to deposit (eg, skin, joints, kidneys) days to weeks after initial antigen exposure in type III hypersensitivity reactions. Although an Arthus reaction can cause local swelling within hours of an exposure, it is usually associated with intradermal injection of a vaccine.

(Choice E) In type IV (delayed) hypersensitivity reactions, $CD4^+$ T cells release cytokines (eg, interferon gamma) that promote T cell- and macrophage-mediated tissue damage. Although these reactions can also present as an indurated skin lesion (eg, tuberculosis skin testing), type IV hypersensitivity reactions develop over days (rather than hours) because of the time needed for cellular amplification.

Educational objective:

The late phase of dermatologic type I hypersensitivity reactions manifests as an indurated skin lesion hours after exposure to the allergen due to local tissue damage caused by major basic protein released from eosinophils. In contrast, type IV hypersensitivity reactions develop over days because of the time needed to produce a cell-mediated immune response.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Wheal and flare

Slightly elevated urticarial lesion (ie, wheal)
Erythema (ie, flare)

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(Choice B) Immune complex-mediated complement activation typically causes tissue damage in sites where immune complexes tend to deposit (eg, skin, joints, kidneys) days to weeks after initial antigen exposure in type III

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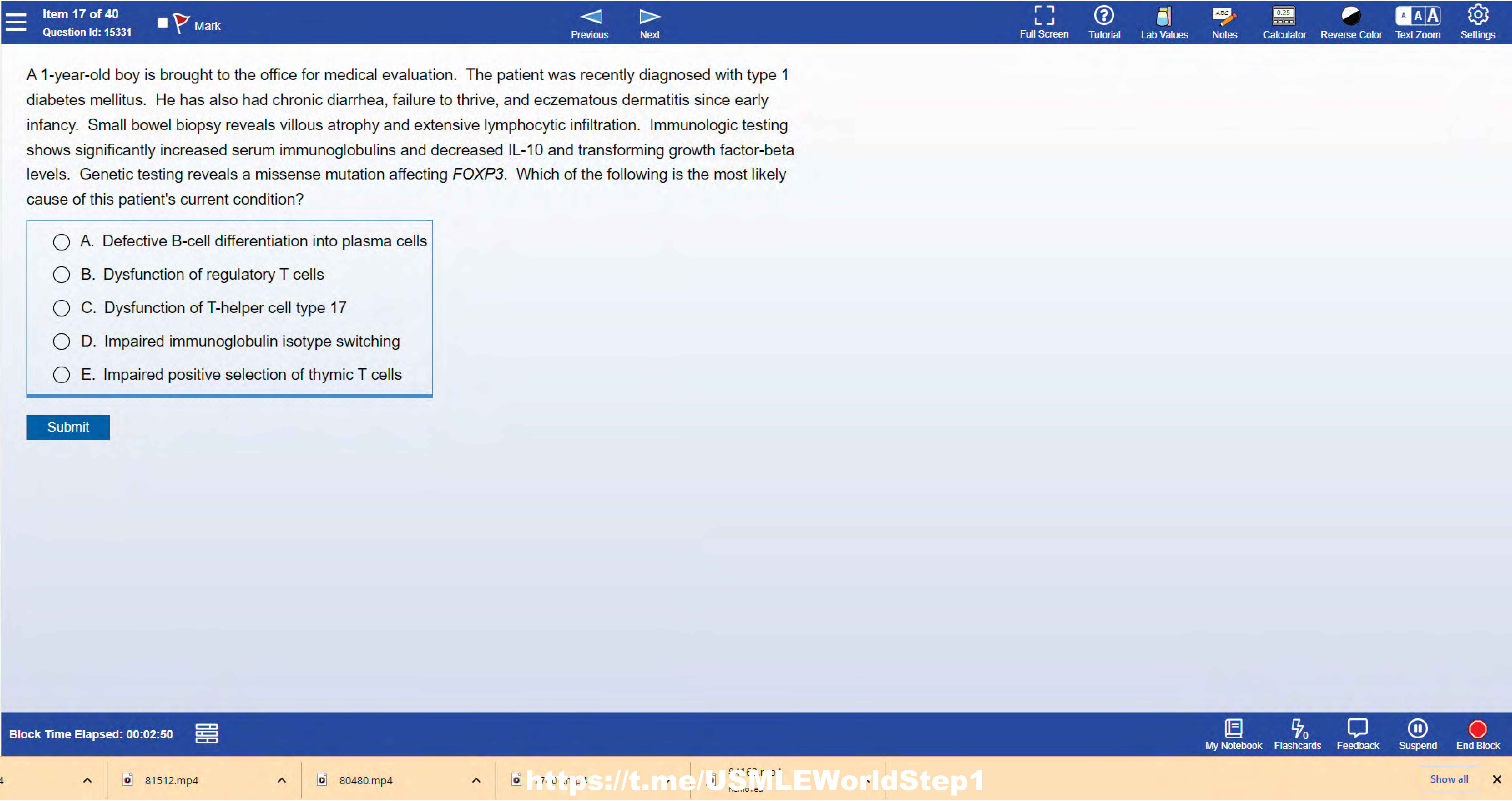
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A 1-year-old boy is brought to the office for medical evaluation. The patient was recently diagnosed with type 1 diabetes mellitus. He has also had chronic diarrhea, failure to thrive, and eczematous dermatitis since early infancy. Small bowel biopsy reveals villous atrophy and extensive lymphocytic infiltration. Immunologic testing shows significantly increased serum immunoglobulins and decreased IL-10 and transforming growth factor-beta levels. Genetic testing reveals a missense mutation affecting *FOXP3*. Which of the following is the most likely cause of this patient's current condition?

- ○ A. Defective B-cell differentiation into plasma cells
- ○ B. Dysfunction of regulatory T cells
- ○ C. Dysfunction of T-helper cell type 17
- ○ D. Impaired immunoglobulin isotype switching
- ○ E. Impaired positive selection of thymic T cells

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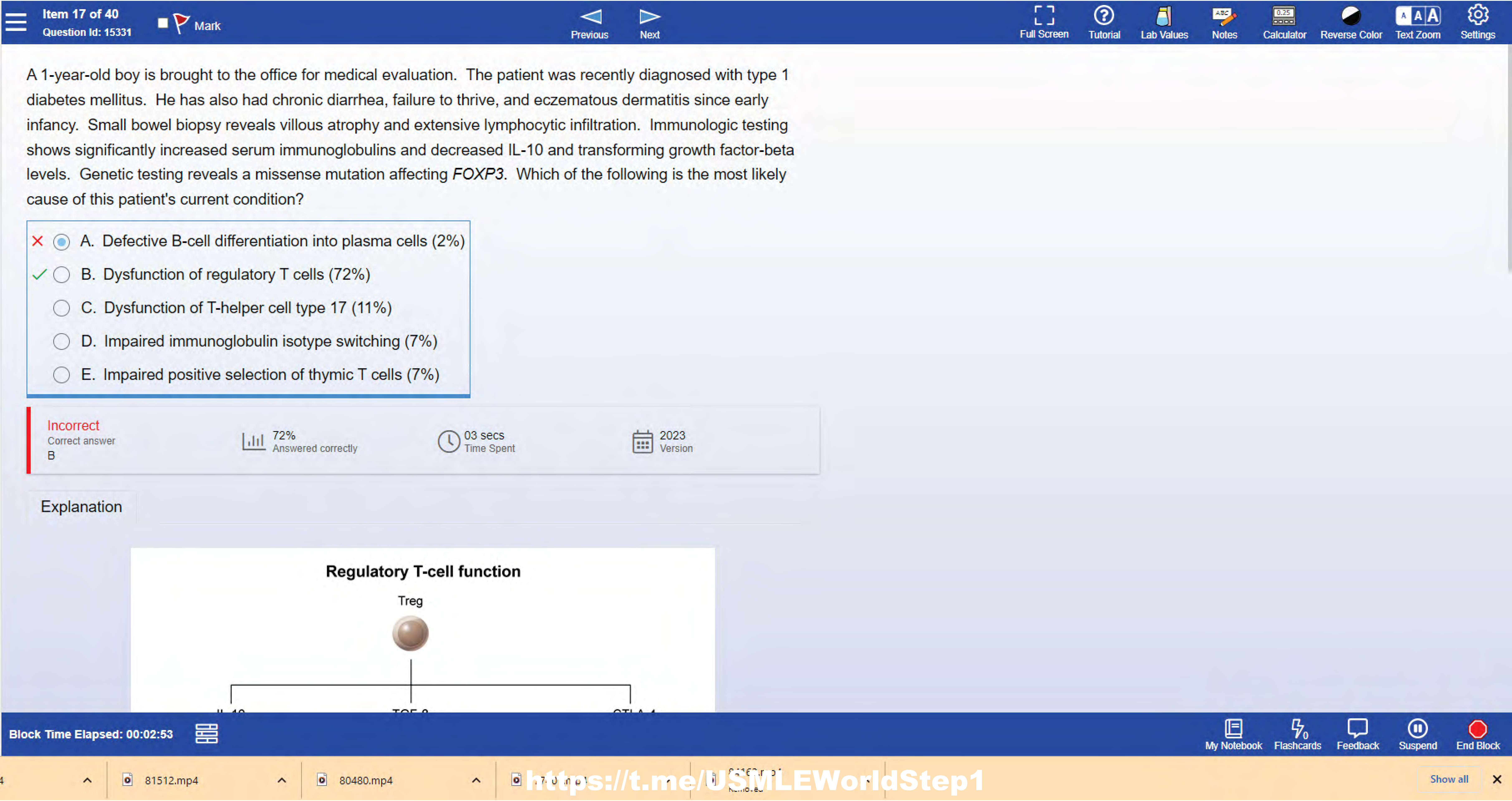

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✗ ● A. Defective B-cell differentiation into plasma cells (2%)

✓ ○ B. Dysfunction of regulatory T cells (72%)

○ C. Dysfunction of T-helper cell type 17 (11%)

○ D. Impaired immunoglobulin isotype switching (7%)

○ E. Impaired positive selection of thymic T cells (7%)

Incorrect
Correct answer
B

72%
Answered correctly

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Explanation

Regulatory T-cell function

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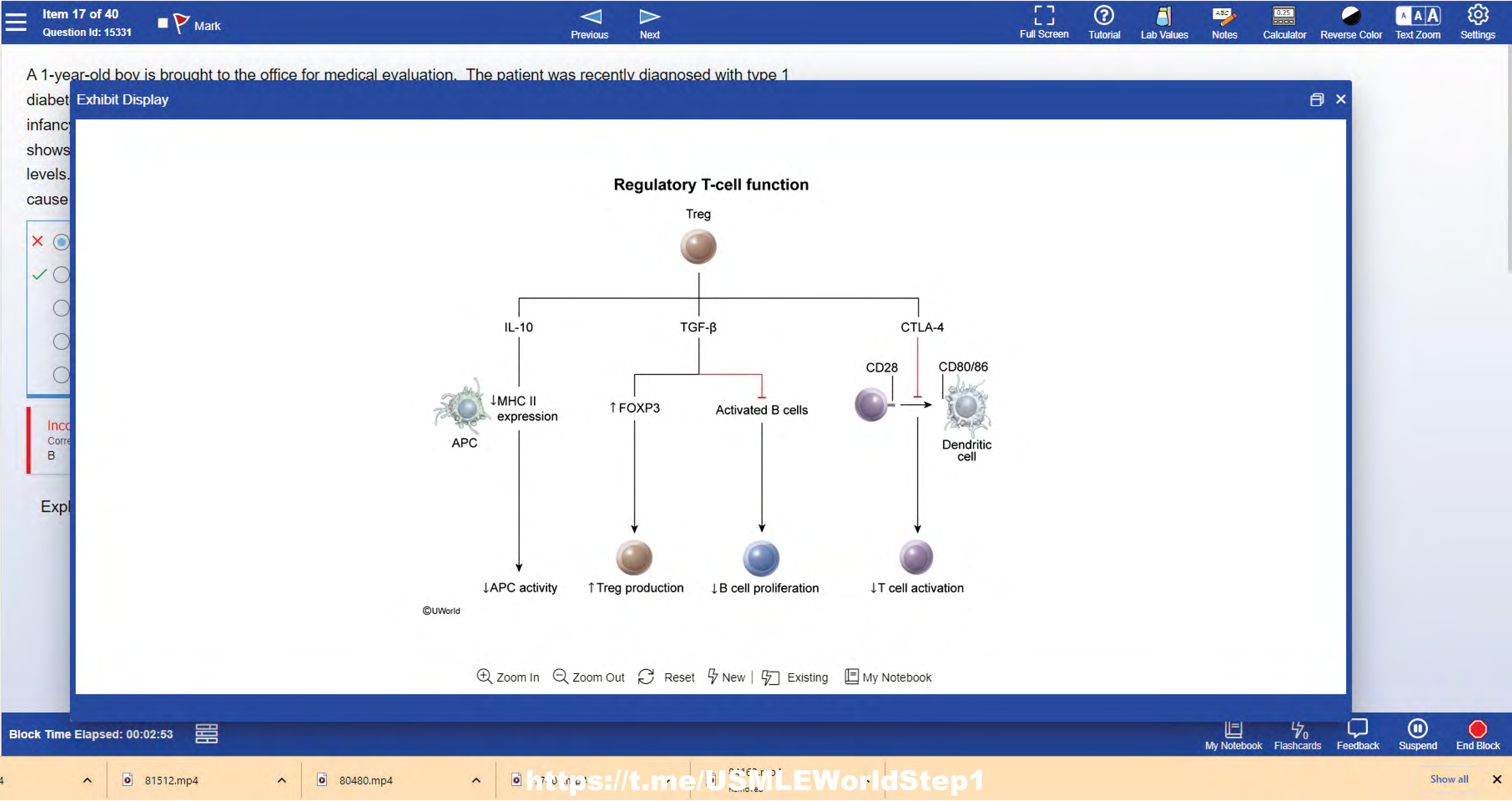
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Regulatory T-cell function

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APC
↑FOXP3
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↓B cell proliferation
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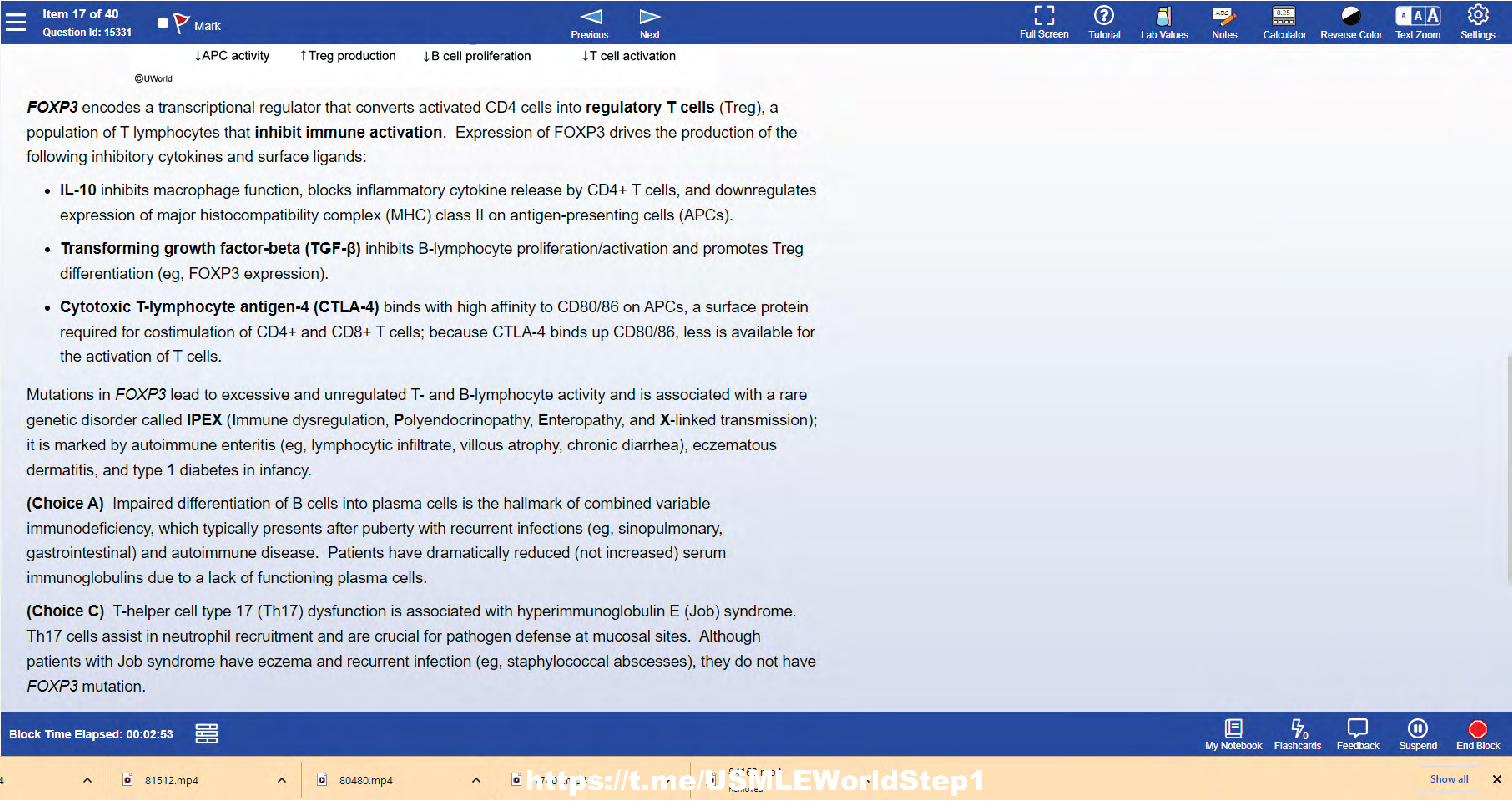
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FOXP3 encodes a transcriptional regulator that converts activated CD4 cells into **regulatory T cells** (Treg), a population of T lymphocytes that **inhibit immune activation**. Expression of FOXP3 drives the production of the following inhibitory cytokines and surface ligands:

- **IL-10** inhibits macrophage function, blocks inflammatory cytokine release by CD4+ T cells, and downregulates expression of major histocompatibility complex (MHC) class II on antigen-presenting cells (APCs).
- **Transforming growth factor-beta (TGF-β)** inhibits B-lymphocyte proliferation/activation and promotes Treg differentiation (eg, FOXP3 expression).
- **Cytotoxic T-lymphocyte antigen-4 (CTLA-4)** binds with high affinity to CD80/86 on APCs, a surface protein required for costimulation of CD4+ and CD8+ T cells; because CTLA-4 binds up CD80/86, less is available for the activation of T cells.

Mutations in *FOXP3* lead to excessive and unregulated T- and B-lymphocyte activity and is associated with a rare genetic disorder called **IPEX** (**I**mmune dysregulation, **P**olyendocrinopathy, **E**nteropathy, and **X**-linked transmission); it is marked by autoimmune enteritis (eg, lymphocytic infiltrate, villous atrophy, chronic diarrhea), eczematous dermatitis, and type 1 diabetes in infancy.

(Choice A) Impaired differentiation of B cells into plasma cells is the hallmark of combined variable immunodeficiency, which typically presents after puberty with recurrent infections (eg, sinopulmonary, gastrointestinal) and autoimmune disease. Patients have dramatically reduced (not increased) serum immunoglobulins due to a lack of functioning plasma cells.

(Choice C) T-helper cell type 17 (Th17) dysfunction is associated with hyperimmunoglobulin E (Job) syndrome. Th17 cells assist in neutrophil recruitment and are crucial for pathogen defense at mucosal sites. Although patients with Job syndrome have eczema and recurrent infection (eg, staphylococcal abscesses), they do not have *FOXP3* mutation.

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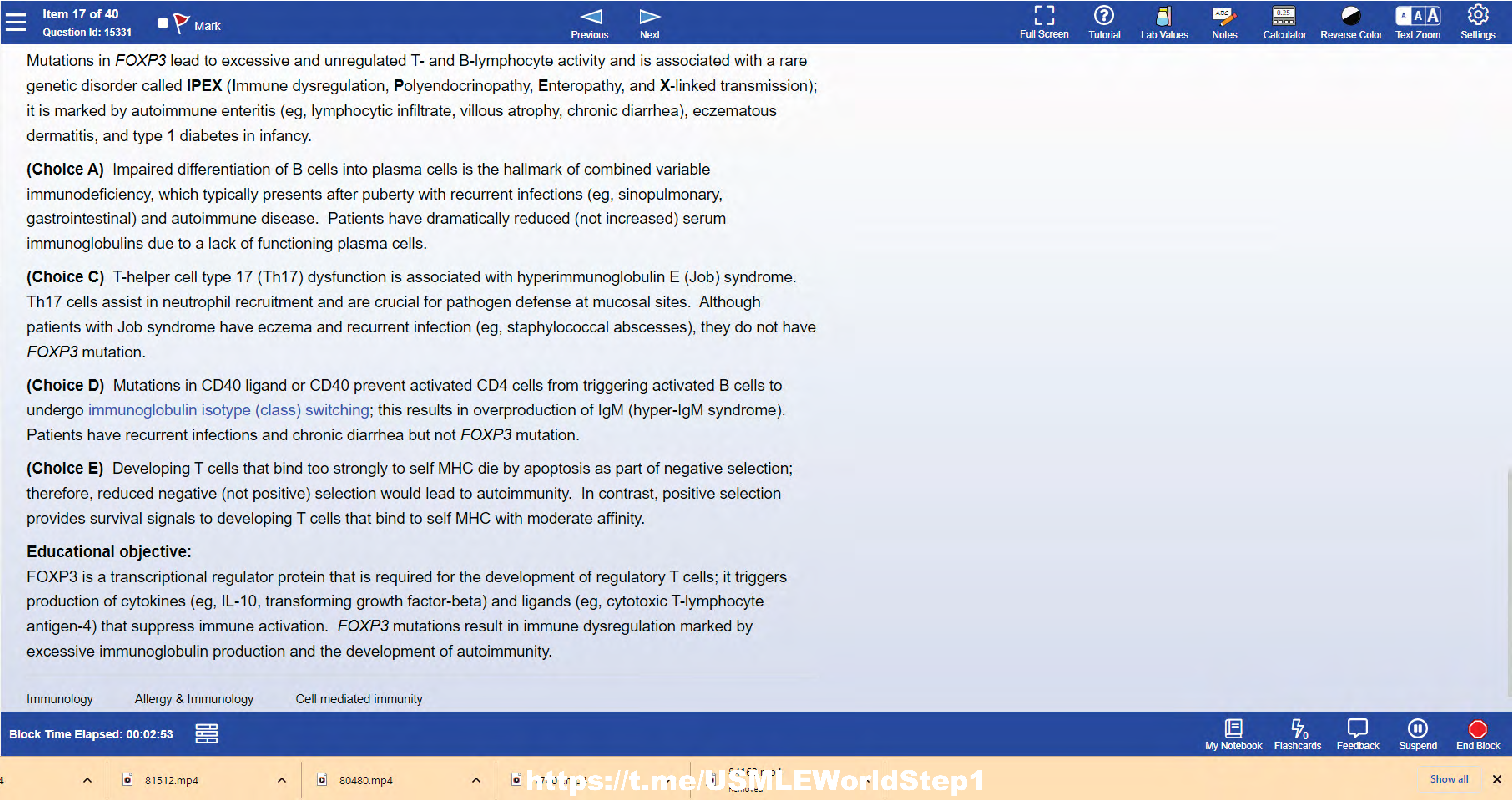

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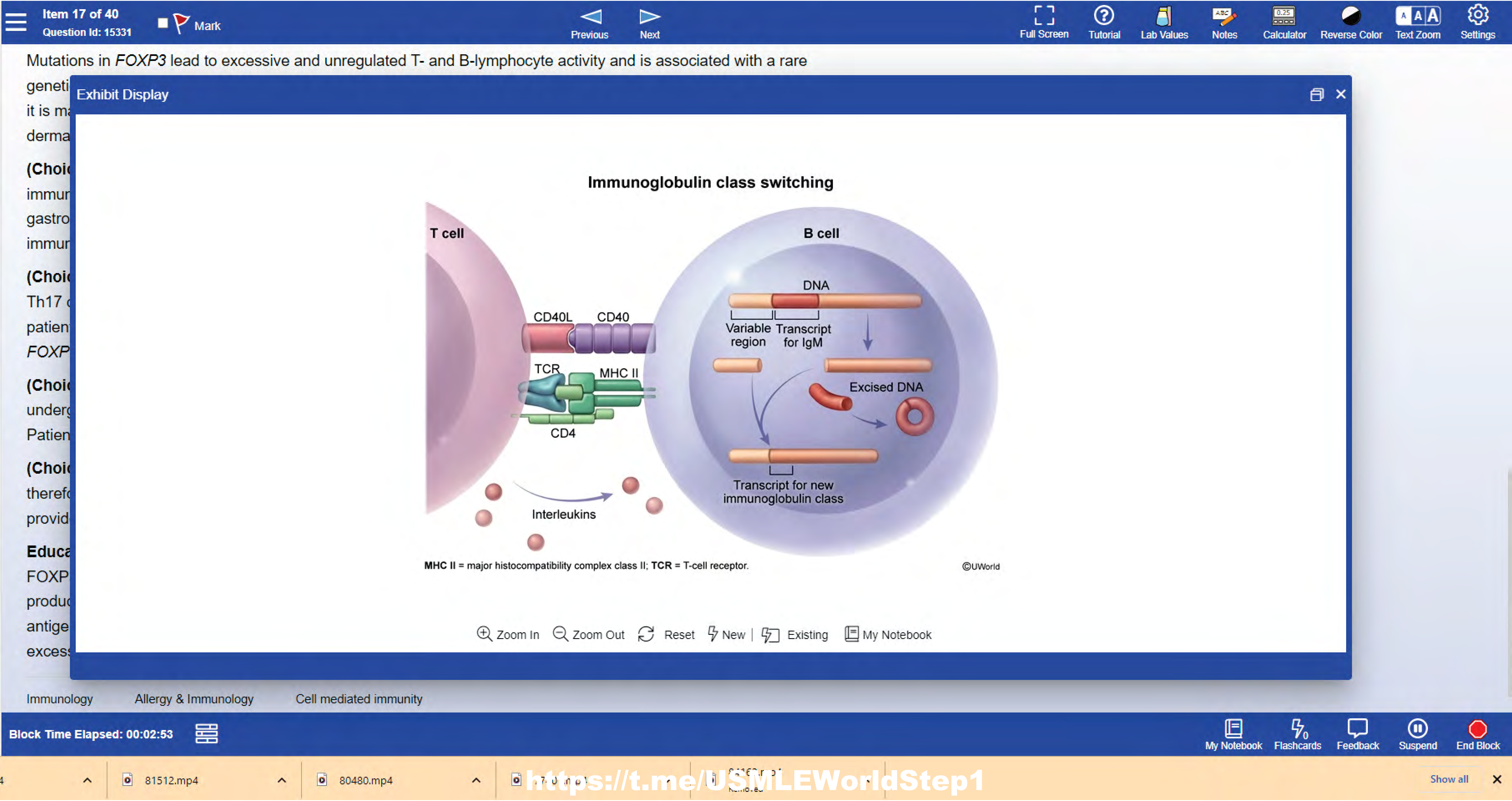
(Choice D) Mutations in CD40 ligand or CD40 prevent activated CD4 cells from triggering activated B cells to undergo immunoglobulin isotype (class) switching; this results in overproduction of IgM (hyper-IgM syndrome). Patients have recurrent infections and chronic diarrhea but not *FOXP3* mutation.

(Choice E) Developing T cells that bind too strongly to self MHC die by apoptosis as part of negative selection; therefore, reduced negative (not positive) selection would lead to autoimmunity. In contrast, positive selection provides survival signals to developing T cells that bind to self MHC with moderate affinity.

Educational objective:
FOXP3 is a transcriptional regulator protein that is required for the development of regulatory T cells; it triggers production of cytokines (eg, IL-10, transforming growth factor-beta) and ligands (eg, cytotoxic T-lymphocyte antigen-4) that suppress immune activation. *FOXP3* mutations result in immune dysregulation marked by excessive immunoglobulin production and the development of autoimmunity.

Immunology   Allergy & Immunology   Cell mediated immunity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Immunoglobulin class switching

MHC II = major histocompatibility complex class II; **TCR** = T-cell receptor.

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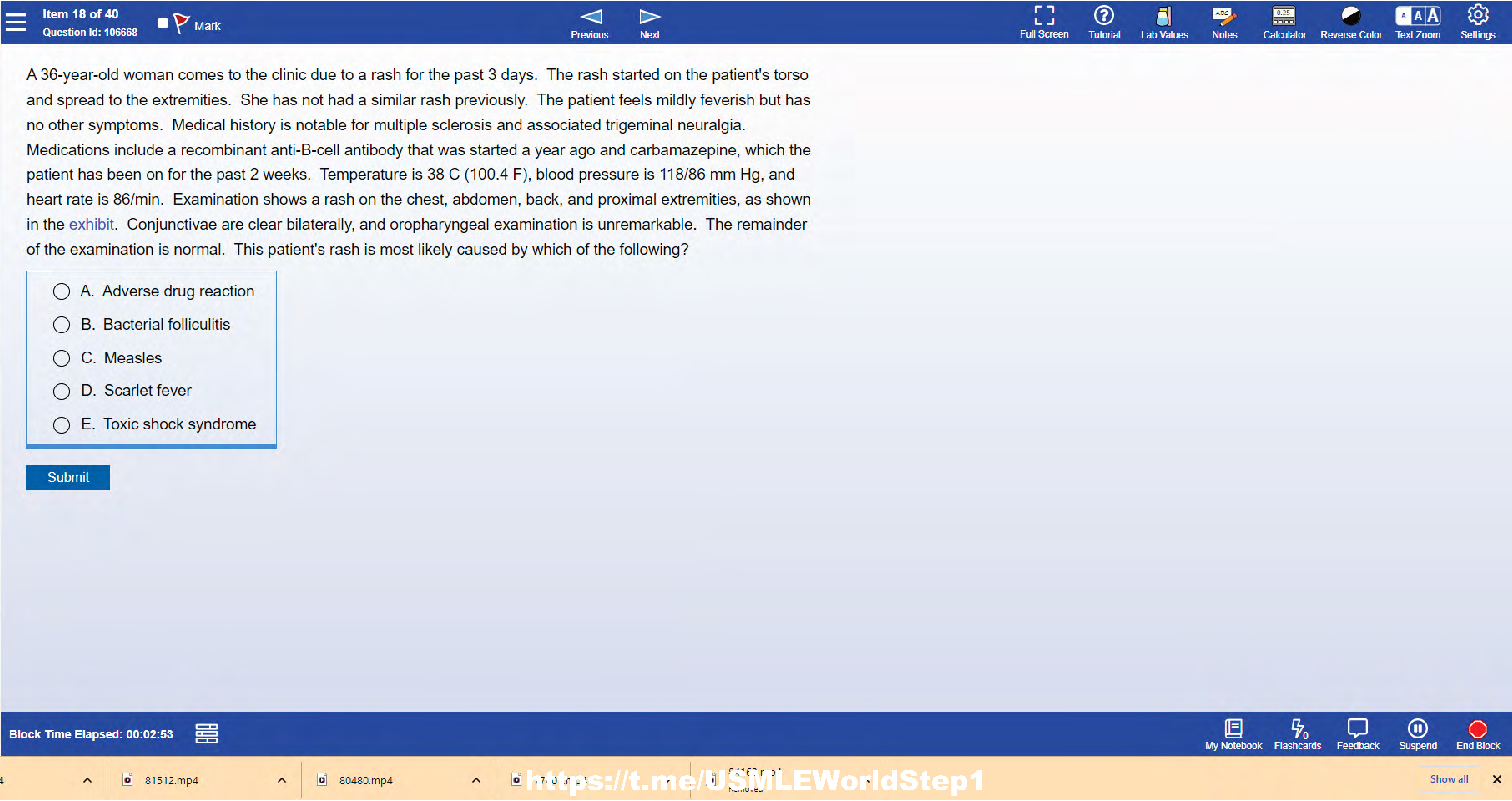
Immunology

Allergy & Immunology

Cell mediated immunity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A 36-year-old woman comes to the clinic due to a rash for the past 3 days. The rash started on the patient's torso and spread to the extremities. She has not had a similar rash previously. The patient feels mildly feverish but has no other symptoms. Medical history is notable for multiple sclerosis and associated trigeminal neuralgia. Medications include a recombinant anti-B-cell antibody that was started a year ago and carbamazepine, which the patient has been on for the past 2 weeks. Temperature is 38 C (100.4 F), blood pressure is 118/86 mm Hg, and heart rate is 86/min. Examination shows a rash on the chest, abdomen, back, and proximal extremities, as shown in the exhibit. Conjunctivae are clear bilaterally, and oropharyngeal examination is unremarkable. The remainder of the examination is normal. This patient's rash is most likely caused by which of the following?

○ A. Adverse drug reaction
○ B. Bacterial folliculitis
○ C. Measles
○ D. Scarlet fever
○ E. Toxic shock syndrome

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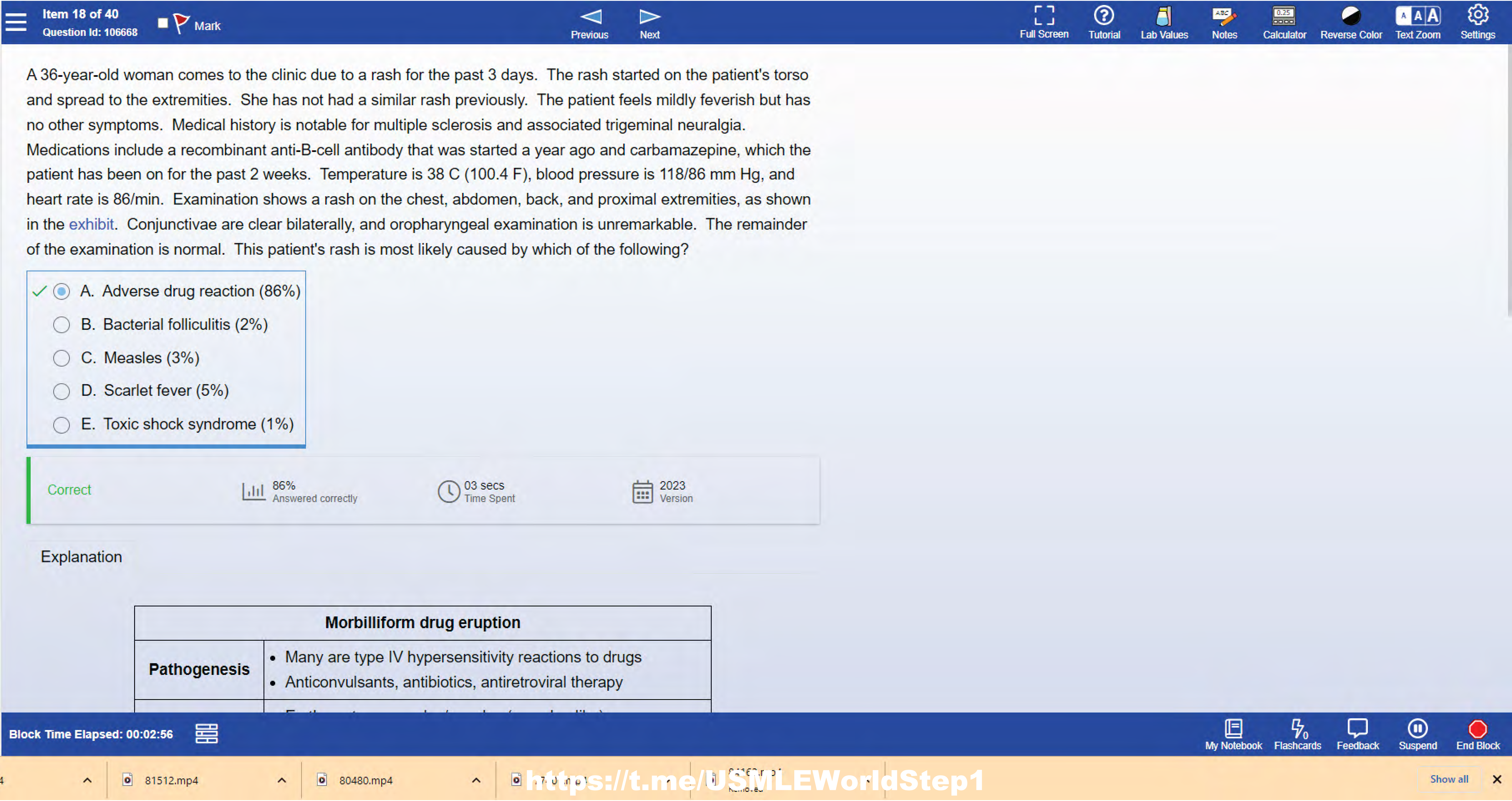
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- ✓ ● A. Adverse drug reaction (86%)
- ○ B. Bacterial folliculitis (2%)
- ○ C. Measles (3%)
- ○ D. Scarlet fever (5%)
- ○ E. Toxic shock syndrome (1%)

Correct

86% Answered correctly

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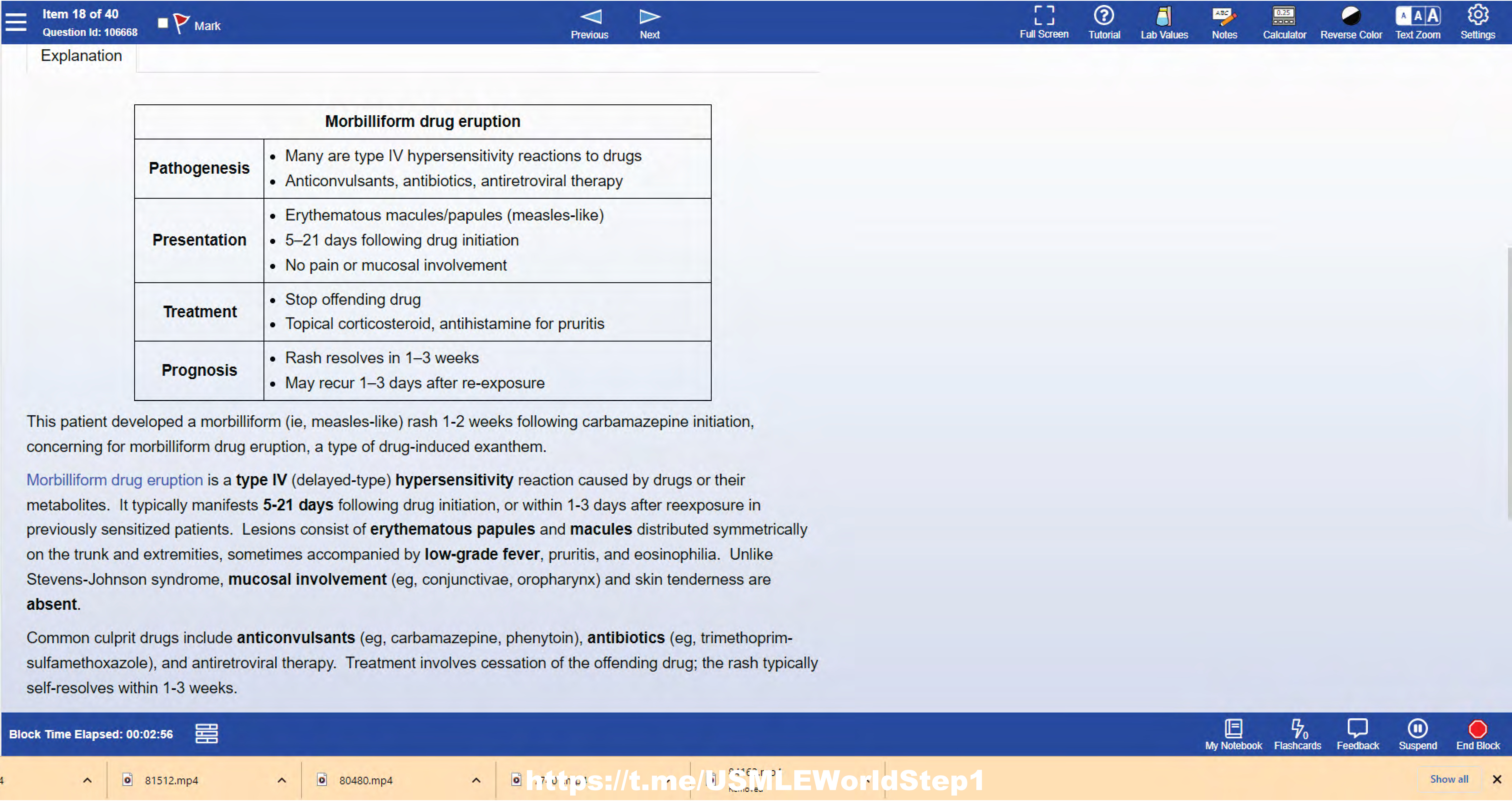
2023 Version

Explanation

Morbilliform drug eruption	
Pathogenesis	• Many are type IV hypersensitivity reactions to drugs • Anticonvulsants, antibiotics, antiretroviral therapy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Explanation

Morbilliform drug eruption	
Pathogenesis	• Many are type IV hypersensitivity reactions to drugs • Anticonvulsants, antibiotics, antiretroviral therapy
Presentation	• Erythematous macules/papules (measles-like) • 5–21 days following drug initiation • No pain or mucosal involvement
Treatment	• Stop offending drug • Topical corticosteroid, antihistamine for pruritis
Prognosis	• Rash resolves in 1–3 weeks • May recur 1–3 days after re-exposure

This patient developed a morbilliform (ie, measles-like) rash 1-2 weeks following carbamazepine initiation, concerning for morbilliform drug eruption, a type of drug-induced exanthem.

Morbilliform drug eruption is a **type IV** (delayed-type) **hypersensitivity** reaction caused by drugs or their metabolites. It typically manifests **5-21 days** following drug initiation, or within 1-3 days after reexposure in previously sensitized patients. Lesions consist of **erythematous papules** and **macules** distributed symmetrically on the trunk and extremities, sometimes accompanied by **low-grade fever**, pruritis, and eosinophilia. Unlike Stevens-Johnson syndrome, **mucosal involvement** (eg, conjunctivae, oropharynx) and skin tenderness are **absent**.

Common culprit drugs include **anticonvulsants** (eg, carbamazepine, phenytoin), **antibiotics** (eg, trimethoprim-sulfamethoxazole), and antiretroviral therapy. Treatment involves cessation of the offending drug; the rash typically self-resolves within 1-3 weeks.

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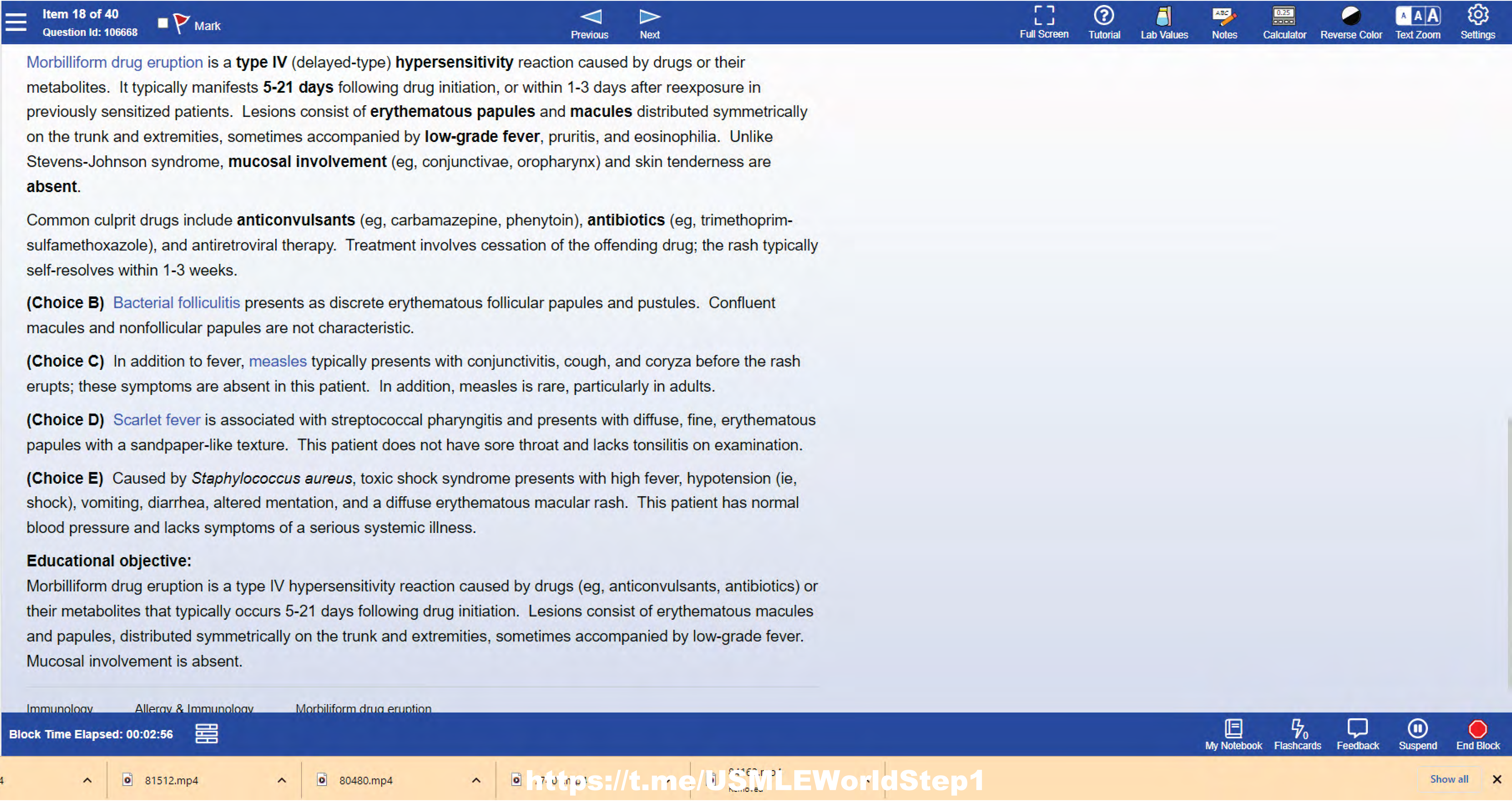

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Common culprit drugs include **anticonvulsants** (eg, carbamazepine, phenytoin), **antibiotics** (eg, trimethoprim-sulfamethoxazole), and antiretroviral therapy. Treatment involves cessation of the offending drug; the rash typically self-resolves within 1-3 weeks.

(Choice B) Bacterial folliculitis presents as discrete erythematous follicular papules and pustules. Confluent macules and nonfollicular papules are not characteristic.

(Choice C) In addition to fever, measles typically presents with conjunctivitis, cough, and coryza before the rash erupts; these symptoms are absent in this patient. In addition, measles is rare, particularly in adults.

(Choice D) Scarlet fever is associated with streptococcal pharyngitis and presents with diffuse, fine, erythematous papules with a sandpaper-like texture. This patient does not have sore throat and lacks tonsilitis on examination.

(Choice E) Caused by *Staphylococcus aureus*, toxic shock syndrome presents with high fever, hypotension (ie, shock), vomiting, diarrhea, altered mentation, and a diffuse erythematous macular rash. This patient has normal blood pressure and lacks symptoms of a serious systemic illness.

Educational objective:

Morbilliform drug eruption is a type IV hypersensitivity reaction caused by drugs (eg, anticonvulsants, antibiotics) or their metabolites that typically occurs 5-21 days following drug initiation. Lesions consist of erythematous macules and papules, distributed symmetrically on the trunk and extremities, sometimes accompanied by low-grade fever. Mucosal involvement is absent.

Immunology Allergy & Immunology Morbilliform drug eruption

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Treatment	- Stop offending drug - Topical corticosteroid, antihistamine for pruritis

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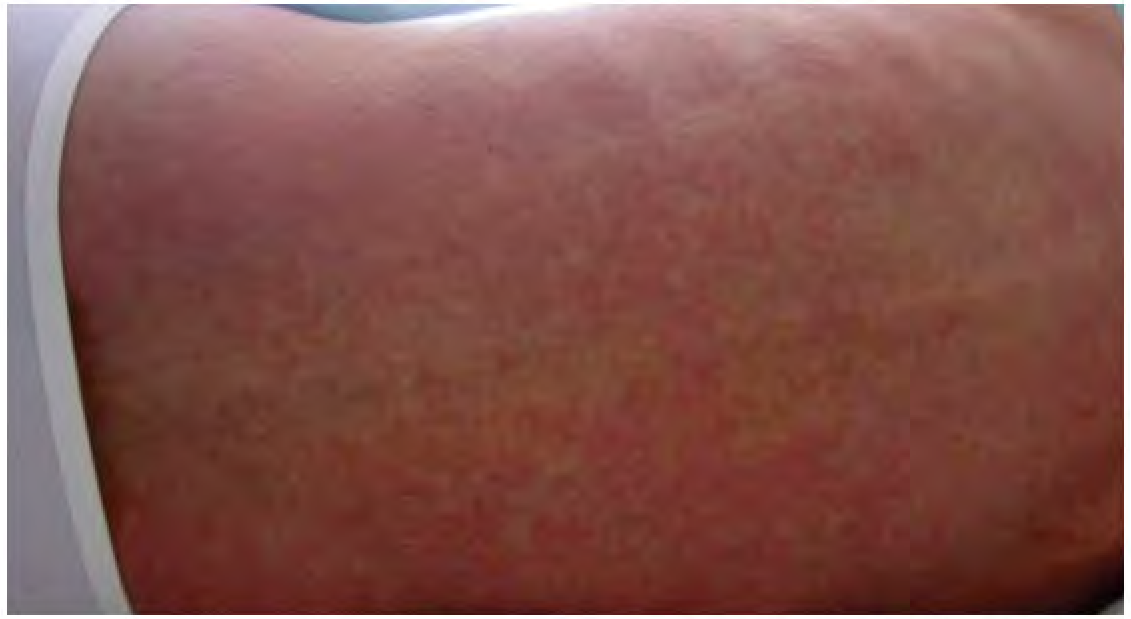
Morbilliform drug eruption



Diffuse, nontender, erythematous macules/papules (measles-like) involving the trunk

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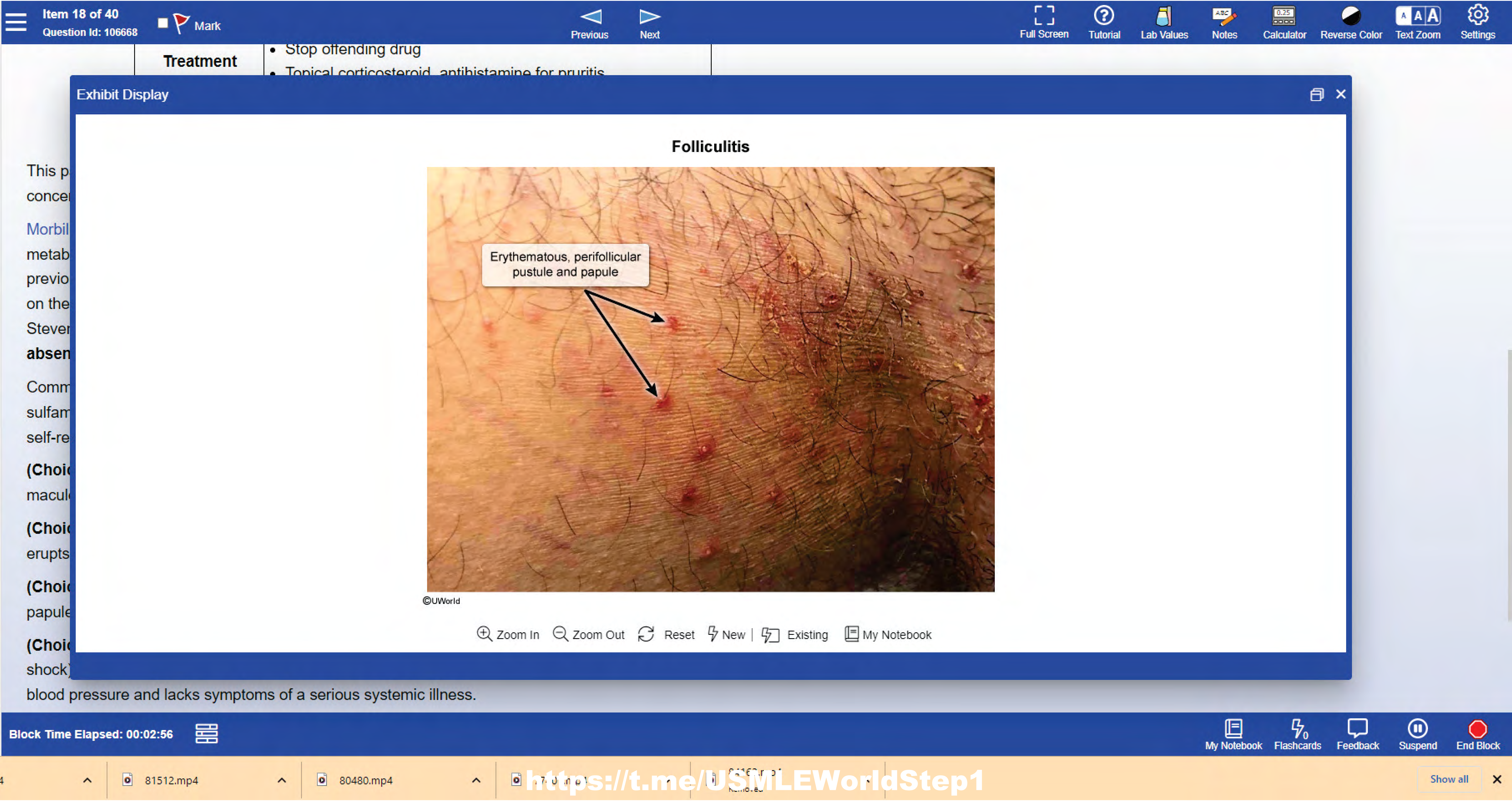
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Treatment	- Stop offending drug - Topical corticosteroid, antihistamine for pruritis

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Erythematous, perifollicular pustule and papule

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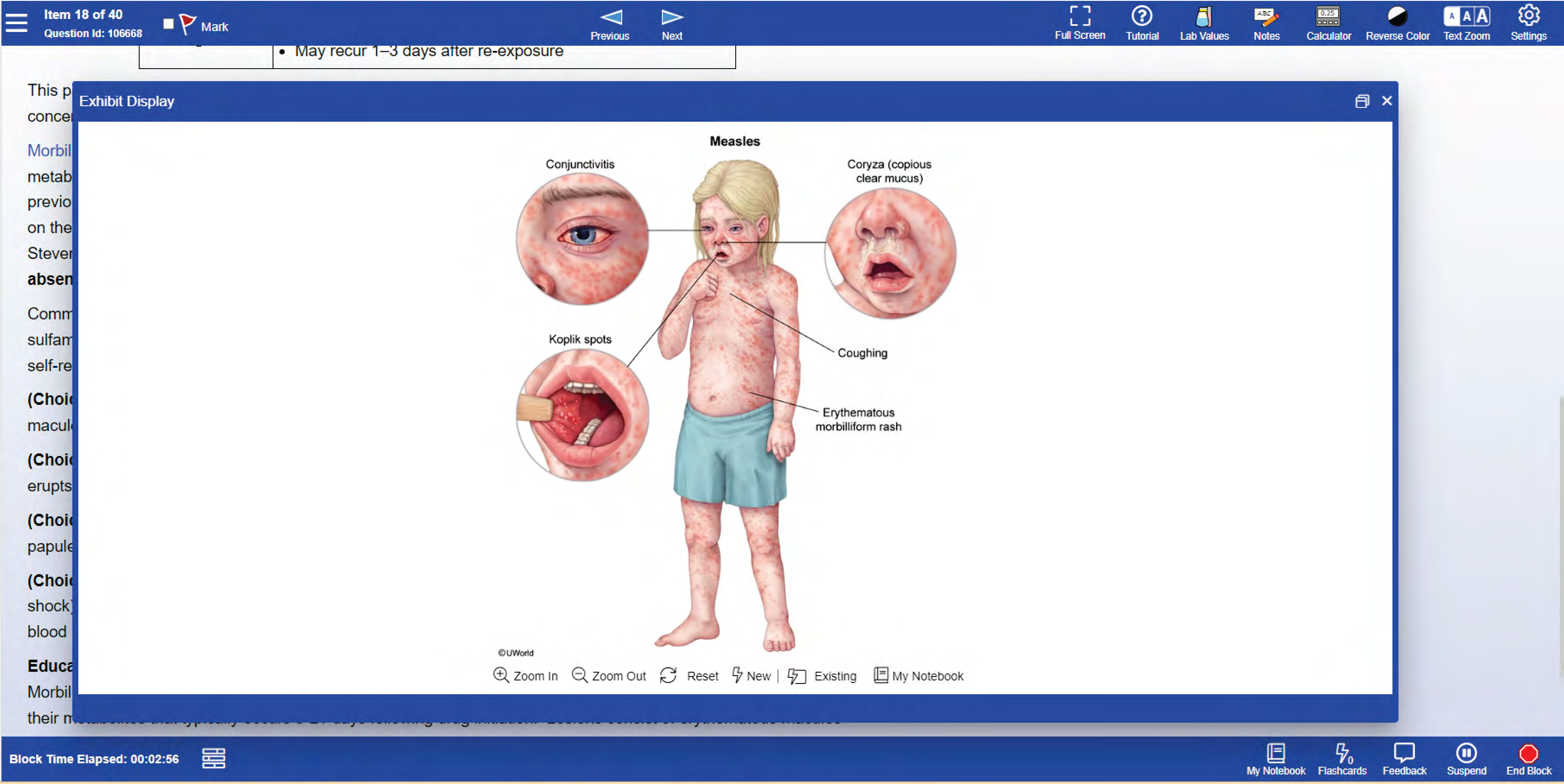

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- May recur 1–3 days after re-exposure

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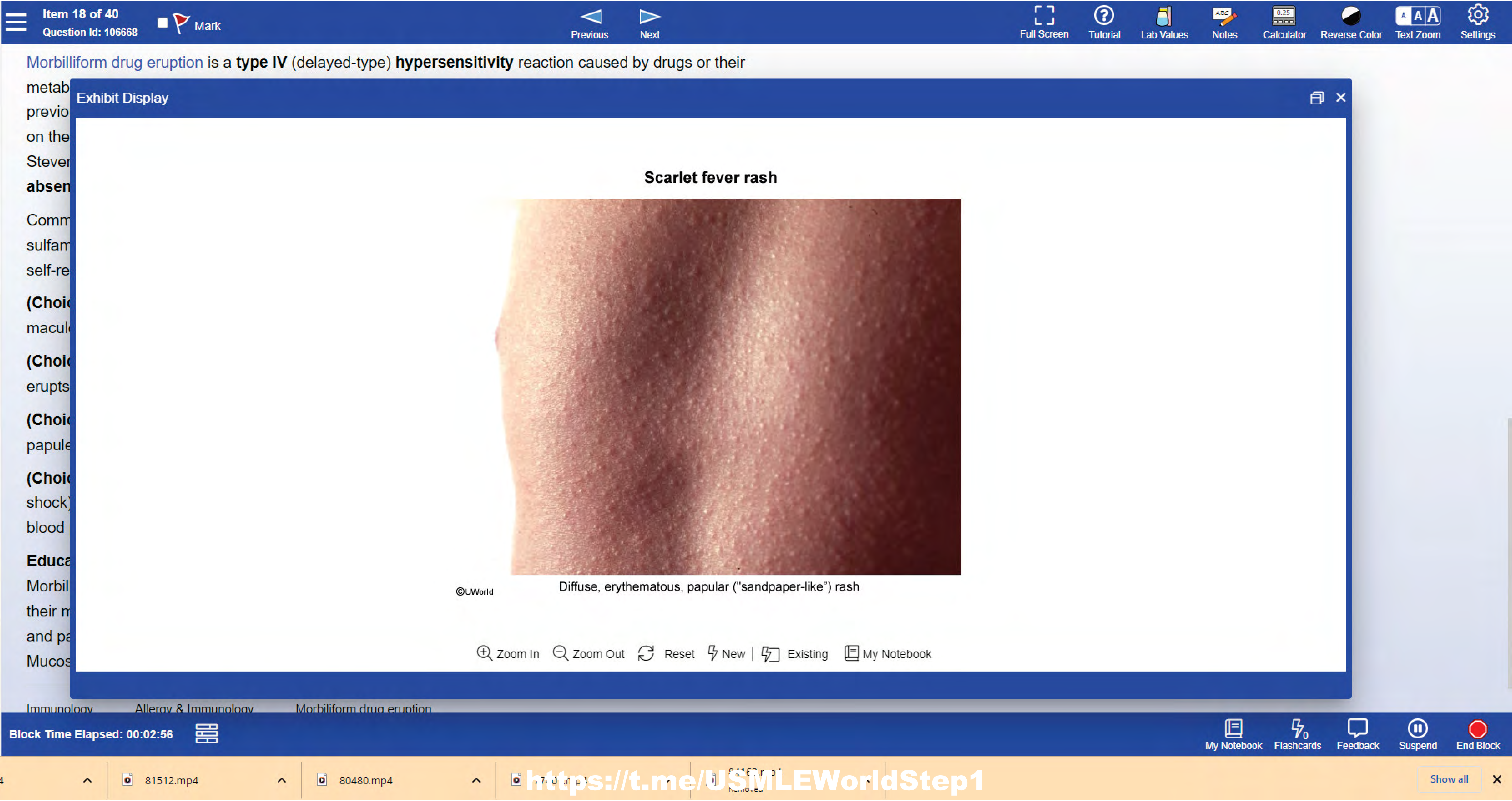
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Morbilliform drug eruption is a **type IV** (delayed-type) **hypersensitivity** reaction caused by drugs or their

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Scarlet fever rash

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Diffuse, erythematous, papular ("sandpaper-like") rash

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Immunology Allergy & Immunology Morbilliform drug eruption

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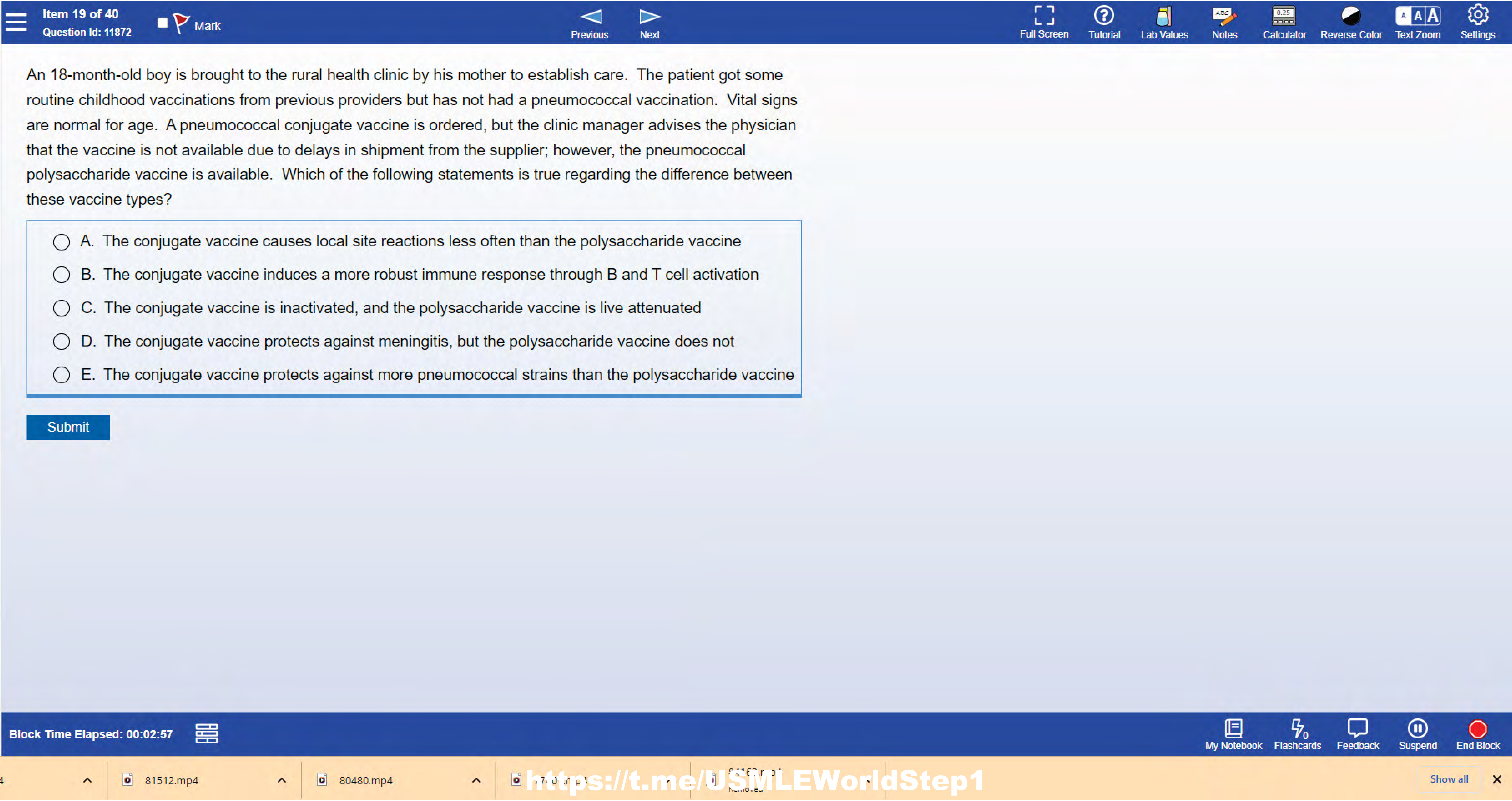
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An 18-month-old boy is brought to the rural health clinic by his mother to establish care. The patient got some routine childhood vaccinations from previous providers but has not had a pneumococcal vaccination. Vital signs are normal for age. A pneumococcal conjugate vaccine is ordered, but the clinic manager advises the physician that the vaccine is not available due to delays in shipment from the supplier; however, the pneumococcal polysaccharide vaccine is available. Which of the following statements is true regarding the difference between these vaccine types?

○ A. The conjugate vaccine causes local site reactions less often than the polysaccharide vaccine

○ B. The conjugate vaccine induces a more robust immune response through B and T cell activation

○ C. The conjugate vaccine is inactivated, and the polysaccharide vaccine is live attenuated

○ D. The conjugate vaccine protects against meningitis, but the polysaccharide vaccine does not

○ E. The conjugate vaccine protects against more pneumococcal strains than the polysaccharide vaccine

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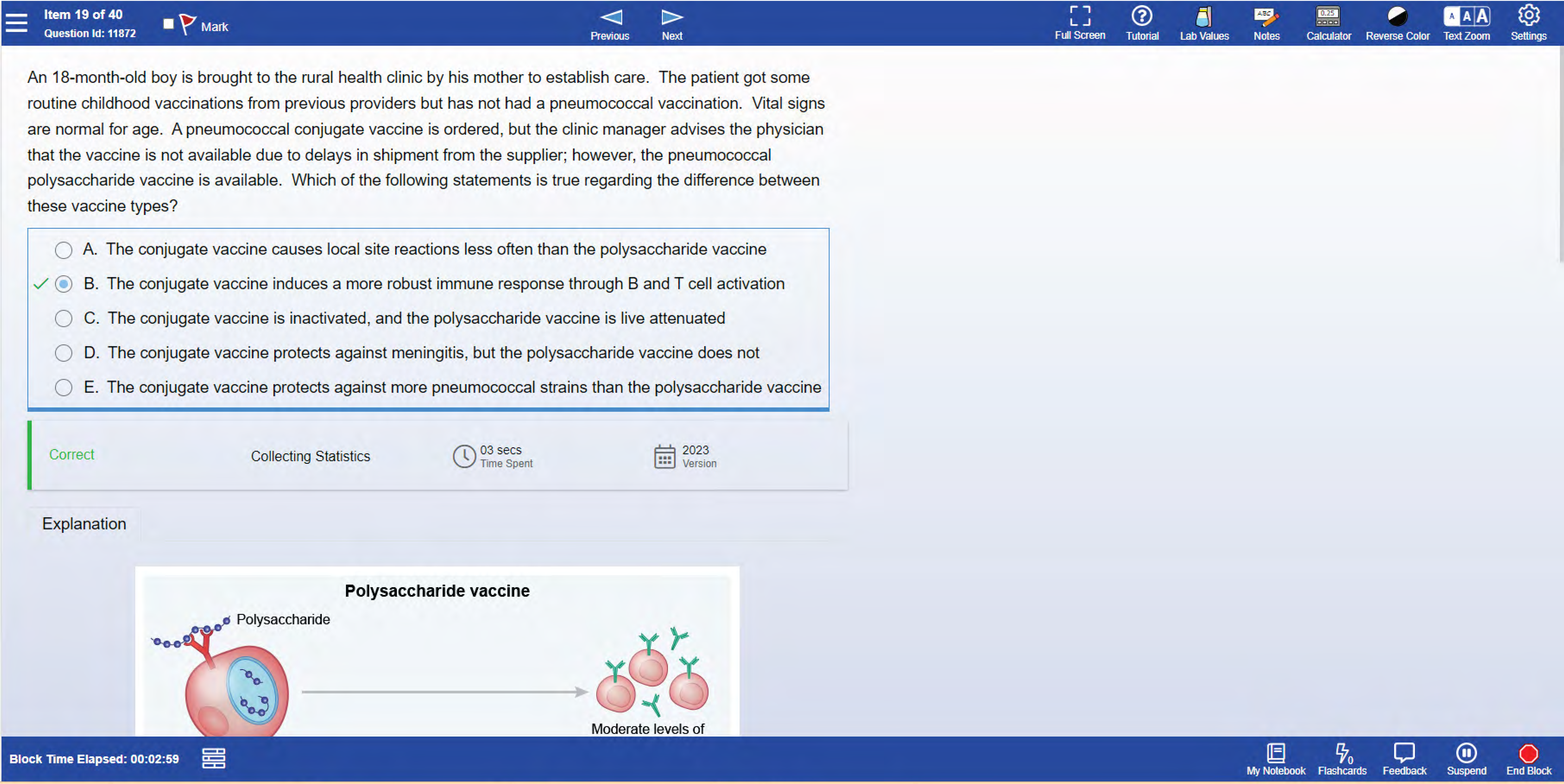
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An 18-month-old boy is brought to the rural health clinic by his mother to establish care. The patient got some routine childhood vaccinations from previous providers but has not had a pneumococcal vaccination. Vital signs are normal for age. A pneumococcal conjugate vaccine is ordered, but the clinic manager advises the physician that the vaccine is not available due to delays in shipment from the supplier; however, the pneumococcal polysaccharide vaccine is available. Which of the following statements is true regarding the difference between these vaccine types?

- ○ A. The conjugate vaccine causes local site reactions less often than the polysaccharide vaccine
- ✓ ● B. The conjugate vaccine induces a more robust immune response through B and T cell activation
- ○ C. The conjugate vaccine is inactivated, and the polysaccharide vaccine is live attenuated
- ○ D. The conjugate vaccine protects against meningitis, but the polysaccharide vaccine does not
- ○ E. The conjugate vaccine protects against more pneumococcal strains than the polysaccharide vaccine

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Explanation

Polysaccharide vaccine

Polysaccharide
Moderate levels of
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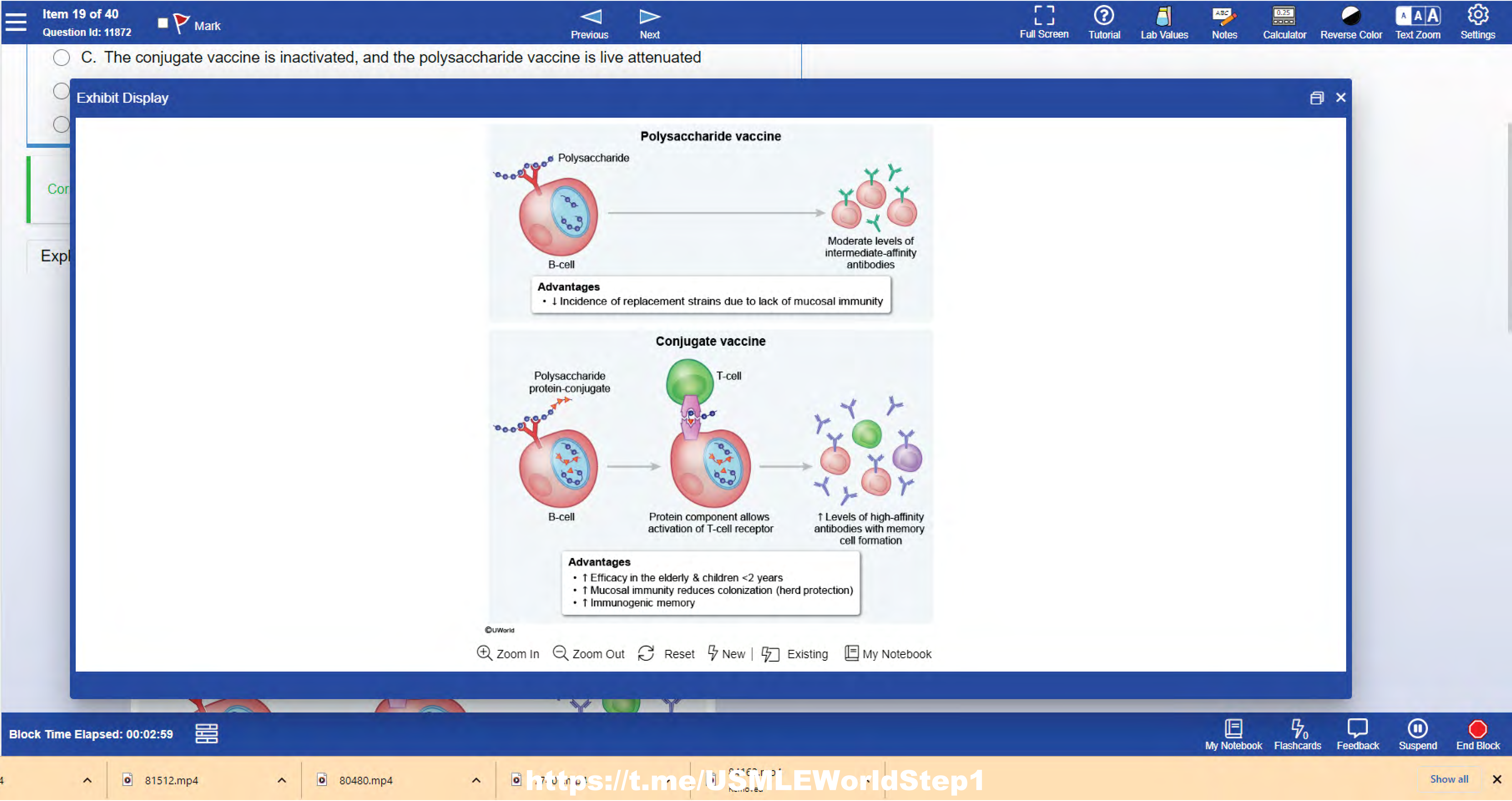
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○ C. The conjugate vaccine is inactivated, and the polysaccharide vaccine is live attenuated

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Polysaccharide vaccine

Polysaccharide
B-cell
Moderate levels of intermediate-affinity antibodies

Advantages
- ↓ Incidence of replacement strains due to lack of mucosal immunity

Conjugate vaccine

Polysaccharide protein-conjugate
T-cell
B-cell
Protein component allows activation of T-cell receptor
↑ Levels of high-affinity antibodies with memory cell formation

Advantages
- ↑ Efficacy in the elderly & children <2 years
- ↑ Mucosal immunity reduces colonization (herd protection)
- ↑ Immunogenic memory

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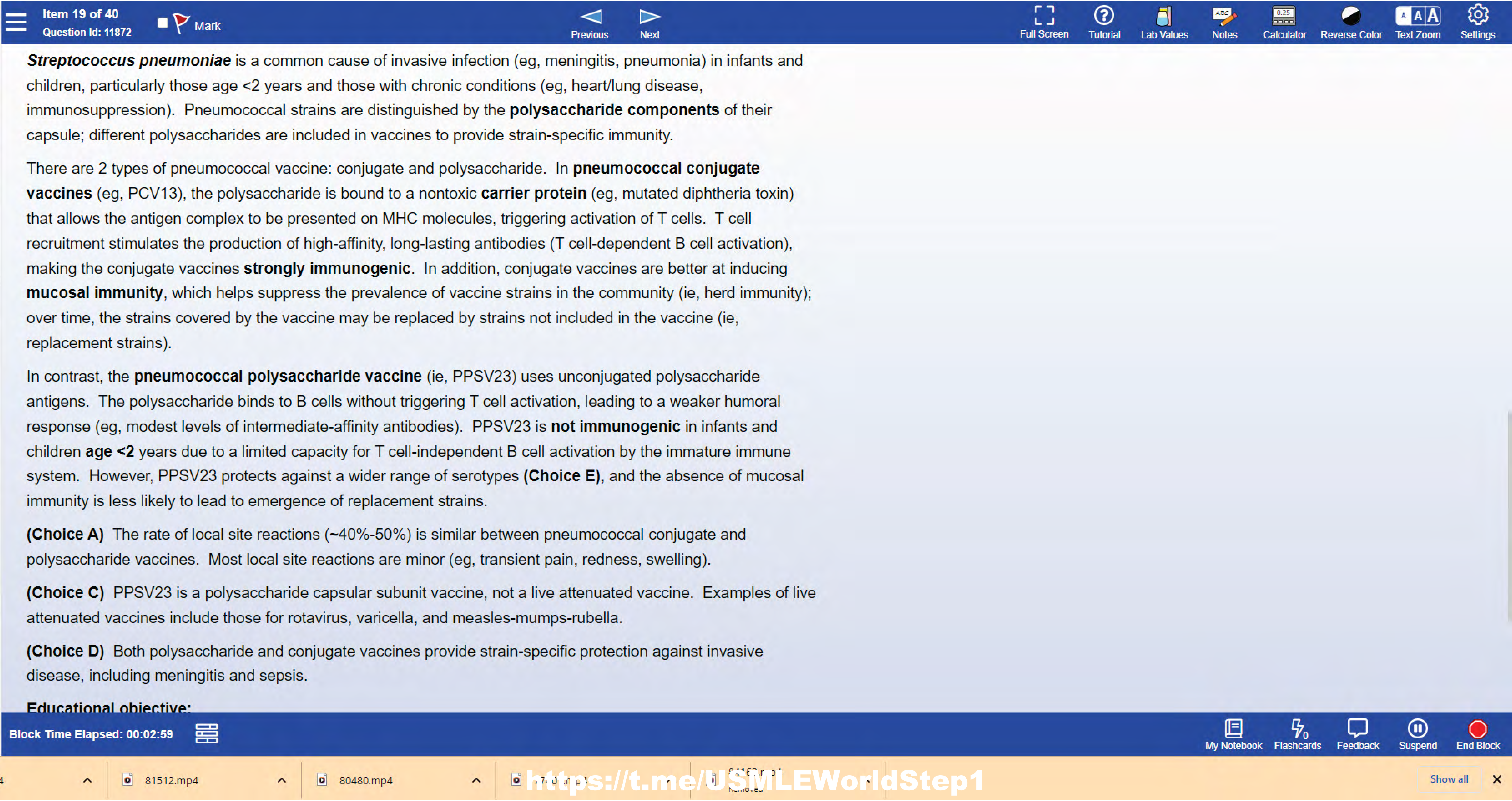


Streptococcus pneumoniae is a common cause of invasive infection (eg, meningitis, pneumonia) in infants and children, particularly those age <2 years and those with chronic conditions (eg, heart/lung disease, immunosuppression). Pneumococcal strains are distinguished by the **polysaccharide components** of their capsule; different polysaccharides are included in vaccines to provide strain-specific immunity.

There are 2 types of pneumococcal vaccine: conjugate and polysaccharide. In **pneumococcal conjugate vaccines** (eg, PCV13), the polysaccharide is bound to a nontoxic **carrier protein** (eg, mutated diphtheria toxin) that allows the antigen complex to be presented on MHC molecules, triggering activation of T cells. T cell recruitment stimulates the production of high-affinity, long-lasting antibodies (T cell-dependent B cell activation), making the conjugate vaccines **strongly immunogenic**. In addition, conjugate vaccines are better at inducing **mucosal immunity**, which helps suppress the prevalence of vaccine strains in the community (ie, herd immunity); over time, the strains covered by the vaccine may be replaced by strains not included in the vaccine (ie, replacement strains).

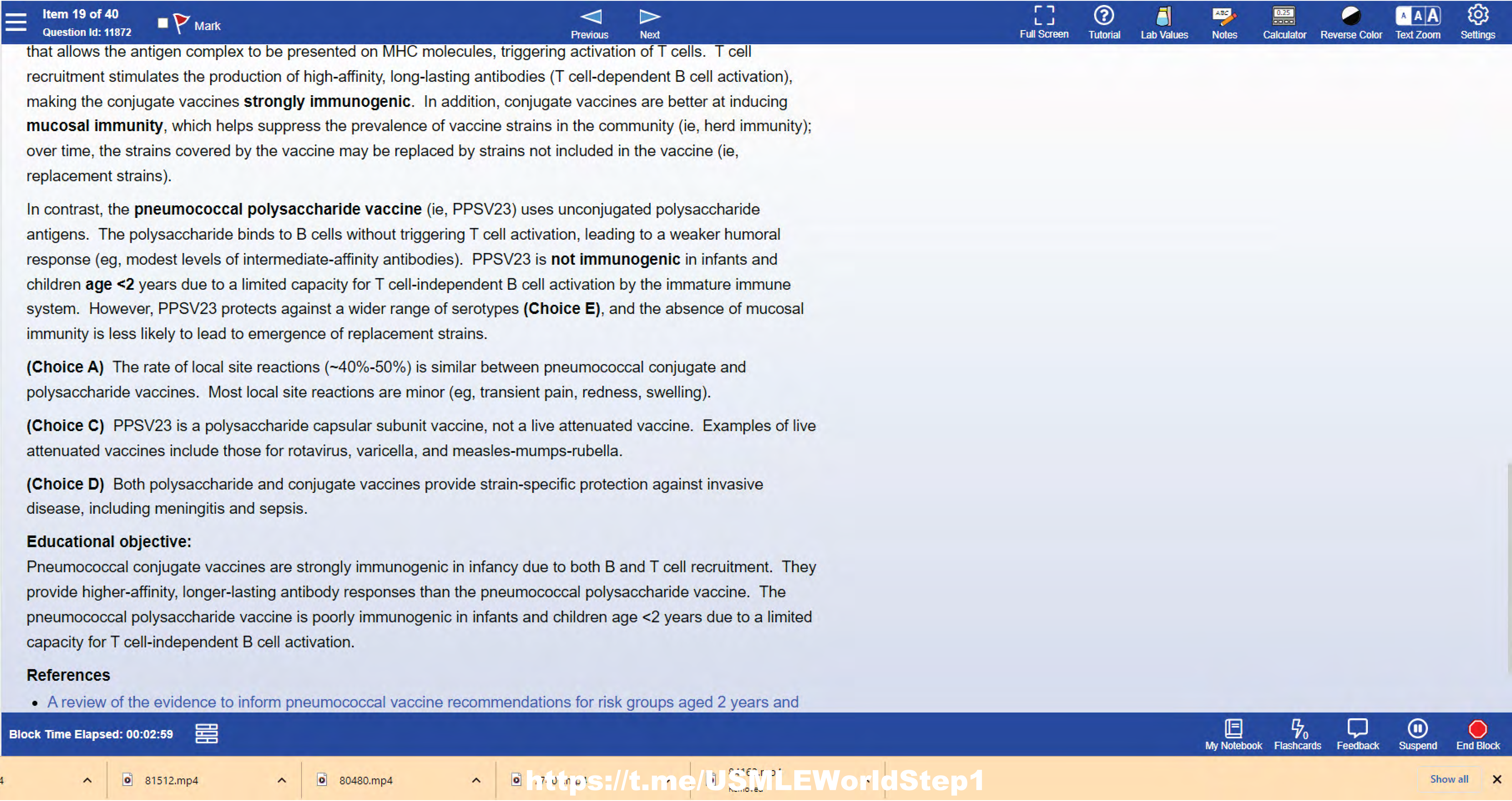
In contrast, the **pneumococcal polysaccharide vaccine** (ie, PPSV23) uses unconjugated polysaccharide antigens. The polysaccharide binds to B cells without triggering T cell activation, leading to a weaker humoral response (eg, modest levels of intermediate-affinity antibodies). PPSV23 is **not immunogenic** in infants and children **age <2** years due to a limited capacity for T cell-independent B cell activation by the immature immune system. However, PPSV23 protects against a wider range of serotypes **(Choice E)**, and the absence of mucosal immunity is less likely to lead to emergence of replacement strains.

(Choice A) The rate of local site reactions (~40%-50%) is similar between pneumococcal conjugate and polysaccharide vaccines. Most local site reactions are minor (eg, transient pain, redness, swelling).

(Choice C) PPSV23 is a polysaccharide capsular subunit vaccine, not a live attenuated vaccine. Examples of live attenuated vaccines include those for rotavirus, varicella, and measles-mumps-rubella.

(Choice D) Both polysaccharide and conjugate vaccines provide strain-specific protection against invasive disease, including meningitis and sepsis.

Educational objective:



that allows the antigen complex to be presented on MHC molecules, triggering activation of T cells. T cell recruitment stimulates the production of high-affinity, long-lasting antibodies (T cell-dependent B cell activation), making the conjugate vaccines **strongly immunogenic**. In addition, conjugate vaccines are better at inducing **mucosal immunity**, which helps suppress the prevalence of vaccine strains in the community (ie, herd immunity); over time, the strains covered by the vaccine may be replaced by strains not included in the vaccine (ie, replacement strains).

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(Choice A) The rate of local site reactions (~40%-50%) is similar between pneumococcal conjugate and polysaccharide vaccines. Most local site reactions are minor (eg, transient pain, redness, swelling).

(Choice C) PPSV23 is a polysaccharide capsular subunit vaccine, not a live attenuated vaccine. Examples of live attenuated vaccines include those for rotavirus, varicella, and measles-mumps-rubella.

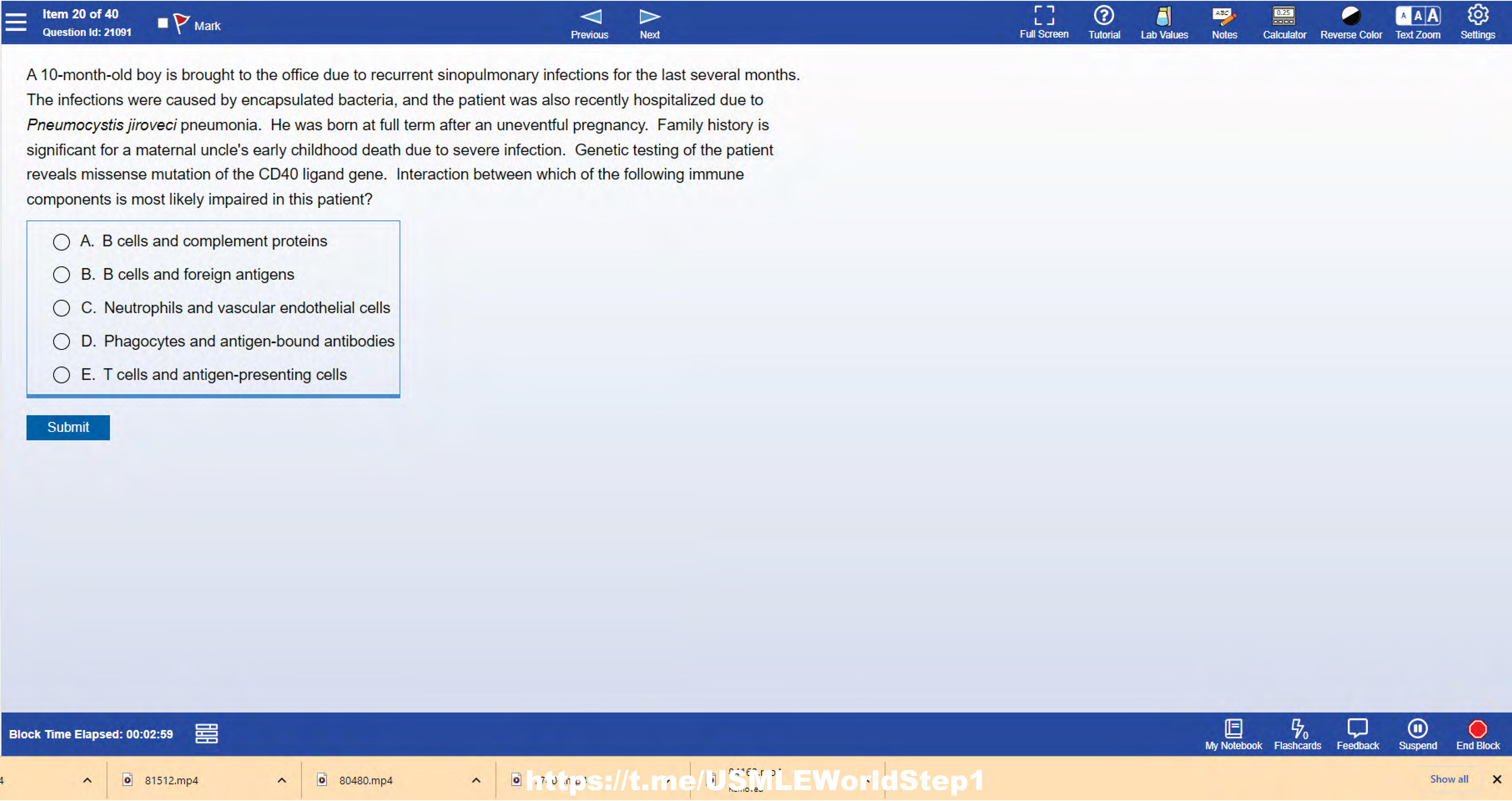
(Choice D) Both polysaccharide and conjugate vaccines provide strain-specific protection against invasive disease, including meningitis and sepsis.

Educational objective:

Pneumococcal conjugate vaccines are strongly immunogenic in infancy due to both B and T cell recruitment. They provide higher-affinity, longer-lasting antibody responses than the pneumococcal polysaccharide vaccine. The pneumococcal polysaccharide vaccine is poorly immunogenic in infants and children age <2 years due to a limited capacity for T cell-independent B cell activation.

References

- A review of the evidence to inform pneumococcal vaccine recommendations for risk groups aged 2 years and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A 10-month-old boy is brought to the office due to recurrent sinopulmonary infections for the last several months. The infections were caused by encapsulated bacteria, and the patient was also recently hospitalized due to *Pneumocystis jiroveci* pneumonia. He was born at full term after an uneventful pregnancy. Family history is significant for a maternal uncle's early childhood death due to severe infection. Genetic testing of the patient reveals missense mutation of the CD40 ligand gene. Interaction between which of the following immune components is most likely impaired in this patient?

○ A. B cells and complement proteins
○ B. B cells and foreign antigens
○ C. Neutrophils and vascular endothelial cells
○ D. Phagocytes and antigen-bound antibodies
○ E. T cells and antigen-presenting cells

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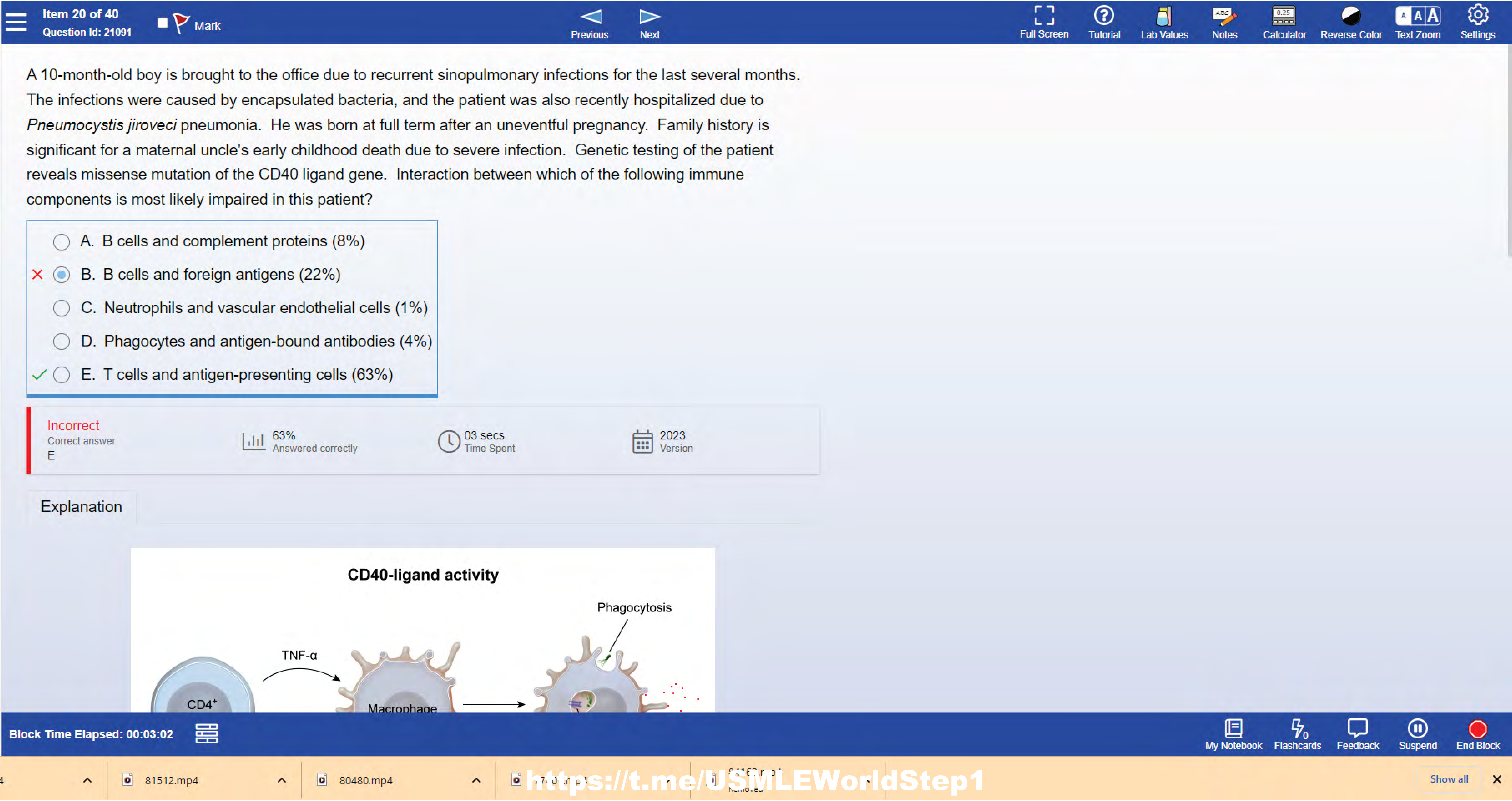
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○ A. B cells and complement proteins (8%)

✗ ● B. B cells and foreign antigens (22%)

○ C. Neutrophils and vascular endothelial cells (1%)

○ D. Phagocytes and antigen-bound antibodies (4%)

✓ ○ E. T cells and antigen-presenting cells (63%)

Incorrect
Correct answer
E

63%
Answered correctly

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Explanation

CD40-ligand activity

Phagocytosis
TNF-α
CD4+
Macrophage

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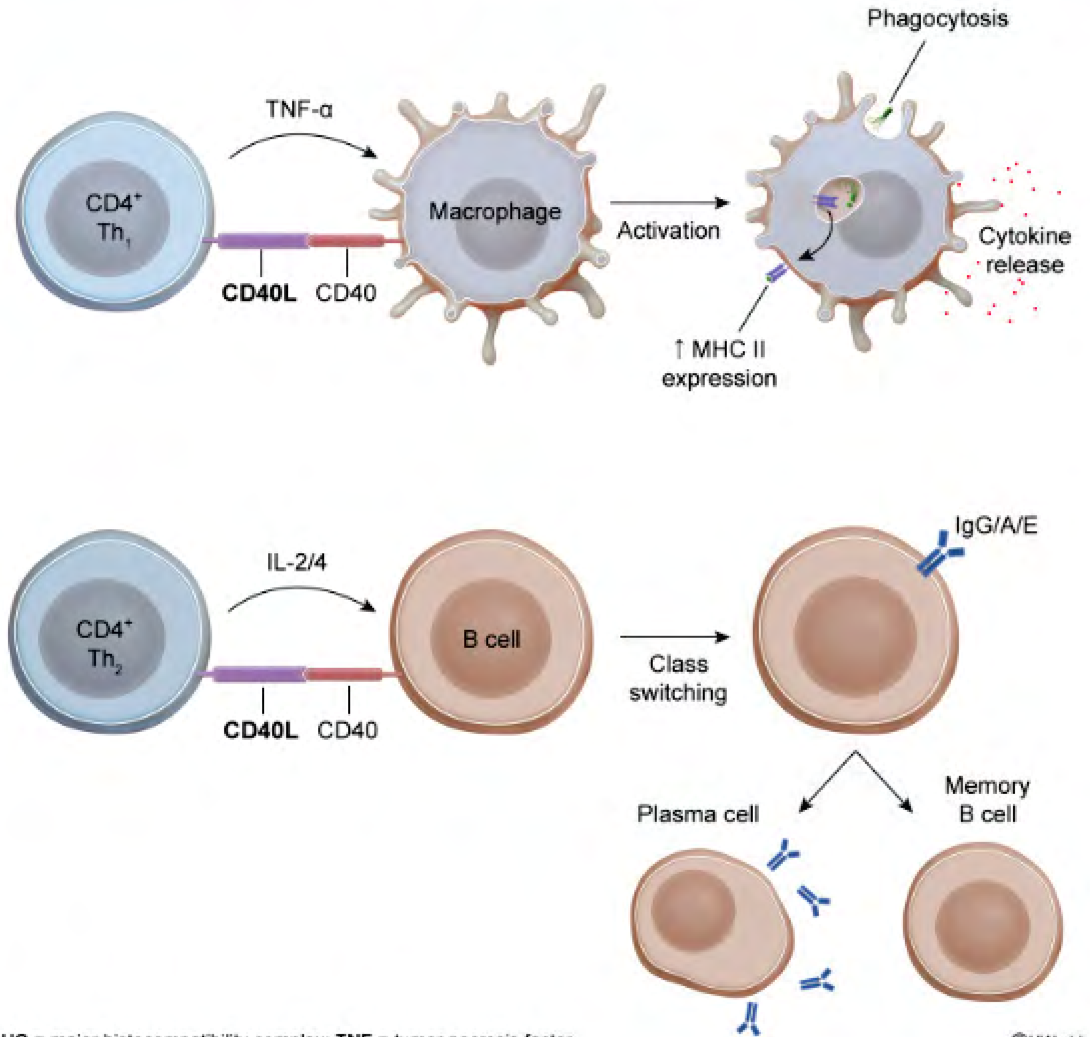
CD40-ligand activity


Phagocytosis
TNF-α
CD4⁺ Th₁
Macrophage
Activation
CD40L
CD40
Cytokine release
↑ MHC II expression
IL-2/4
CD4⁺ Th₂
B cell
IgG/A/E
Class switching
Plasma cell
Memory B cell

MHC = major histocompatibility complex; **TNF** = tumor necrosis factor.

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TNF-α
CD4⁺
Macrophage

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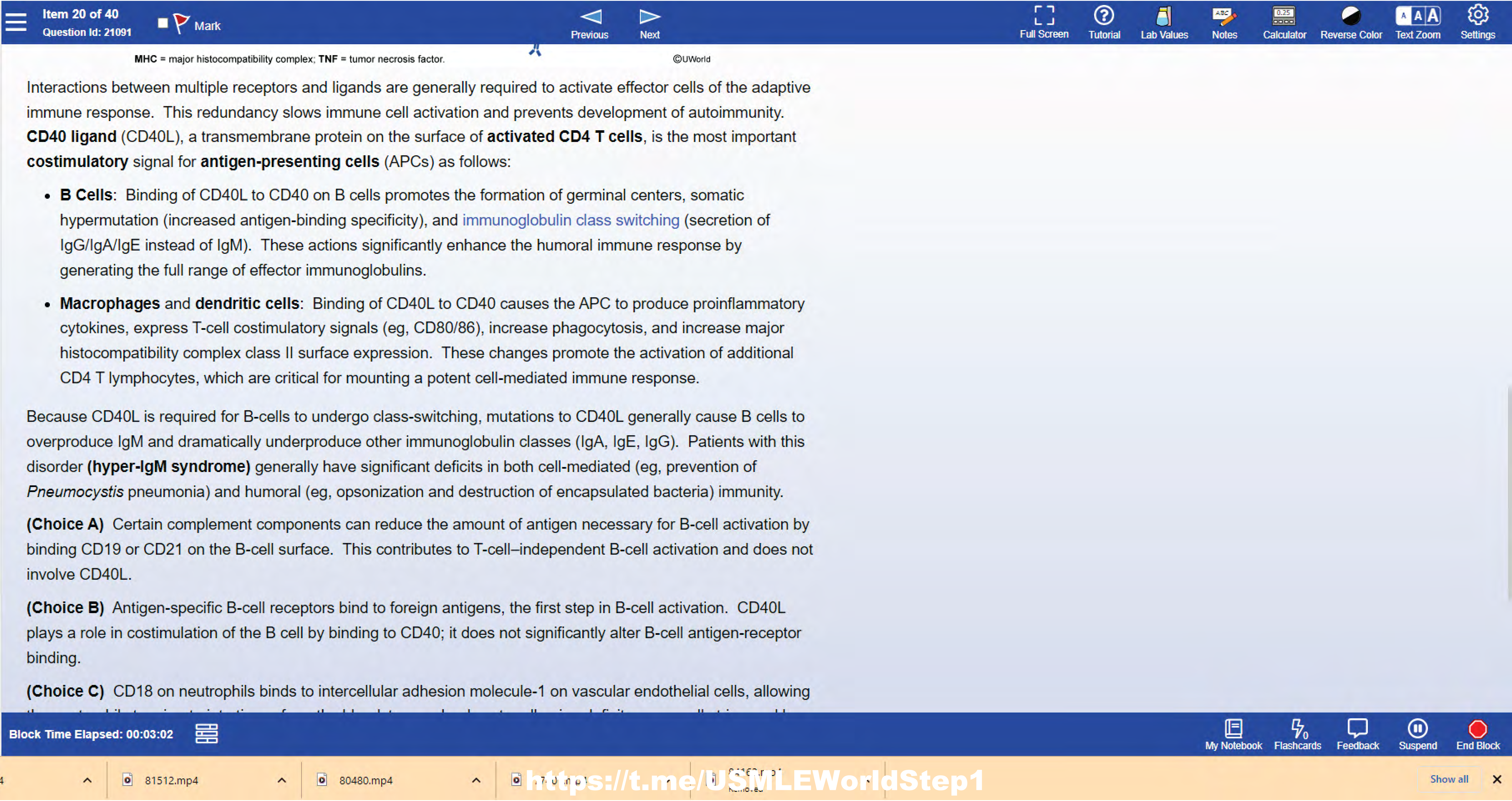

MHC = major histocompatibility complex; **TNF** = tumor necrosis factor.

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Interactions between multiple receptors and ligands are generally required to activate effector cells of the adaptive immune response. This redundancy slows immune cell activation and prevents development of autoimmunity. **CD40 ligand** (CD40L), a transmembrane protein on the surface of **activated CD4 T cells**, is the most important **costimulatory** signal for **antigen-presenting cells** (APCs) as follows:

- **B Cells**: Binding of CD40L to CD40 on B cells promotes the formation of germinal centers, somatic hypermutation (increased antigen-binding specificity), and immunoglobulin class switching (secretion of IgG/IgA/IgE instead of IgM). These actions significantly enhance the humoral immune response by generating the full range of effector immunoglobulins.
- **Macrophages** and **dendritic cells**: Binding of CD40L to CD40 causes the APC to produce proinflammatory cytokines, express T-cell costimulatory signals (eg, CD80/86), increase phagocytosis, and increase major histocompatibility complex class II surface expression. These changes promote the activation of additional CD4 T lymphocytes, which are critical for mounting a potent cell-mediated immune response.

Because CD40L is required for B-cells to undergo class-switching, mutations to CD40L generally cause B cells to overproduce IgM and dramatically underproduce other immunoglobulin classes (IgA, IgE, IgG). Patients with this disorder **(hyper-IgM syndrome)** generally have significant deficits in both cell-mediated (eg, prevention of *Pneumocystis* pneumonia) and humoral (eg, opsonization and destruction of encapsulated bacteria) immunity.

(Choice A) Certain complement components can reduce the amount of antigen necessary for B-cell activation by binding CD19 or CD21 on the B-cell surface. This contributes to T-cell–independent B-cell activation and does not involve CD40L.

(Choice B) Antigen-specific B-cell receptors bind to foreign antigens, the first step in B-cell activation. CD40L plays a role in costimulation of the B cell by binding to CD40; it does not significantly alter B-cell antigen-receptor binding.

(Choice C) CD18 on neutrophils binds to intercellular adhesion molecule-1 on vascular endothelial cells, allowing

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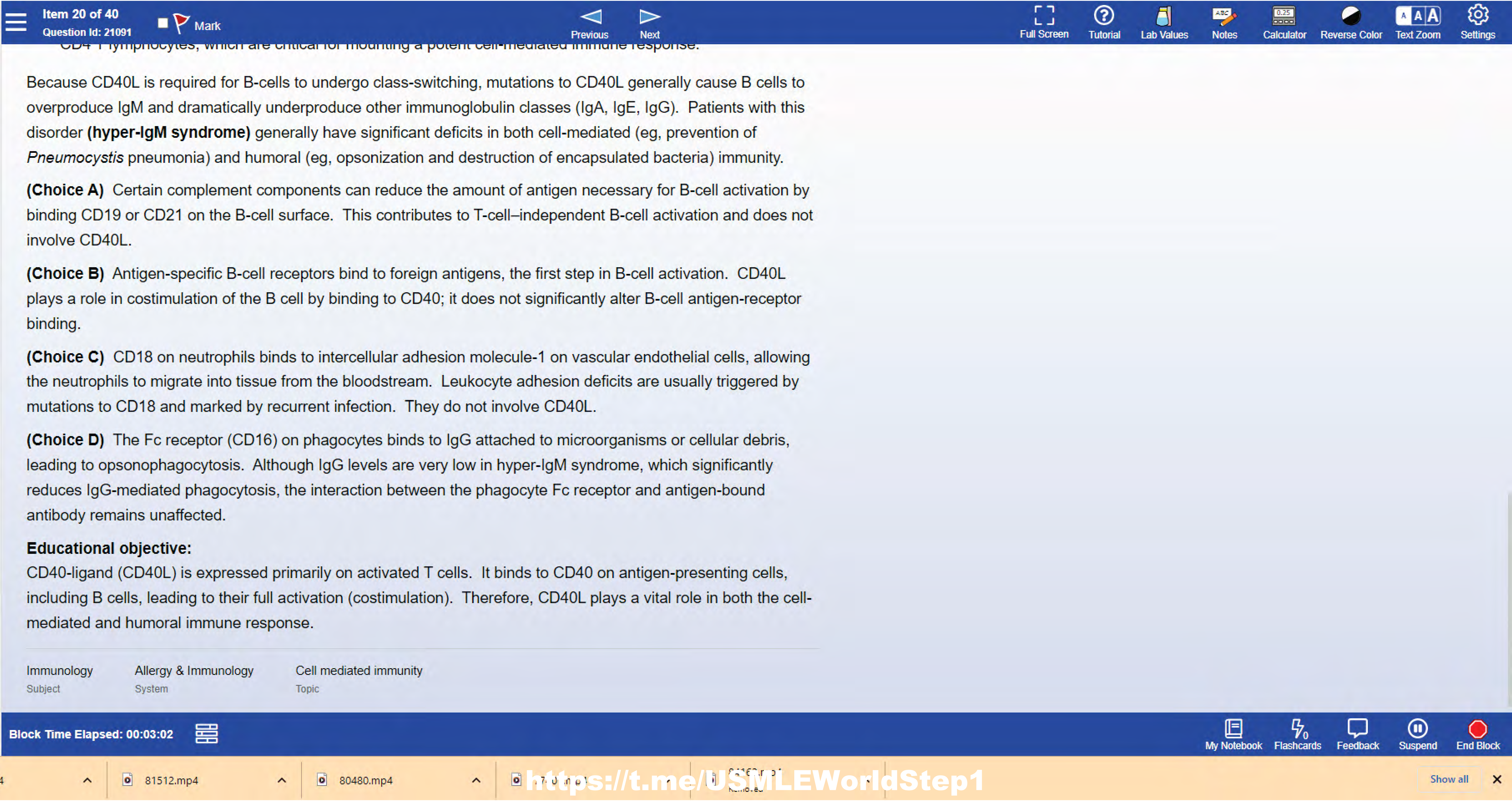

CD4 T lymphocytes, which are critical for mounting a potent cell-mediated immune response.

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(Choice B) Antigen-specific B-cell receptors bind to foreign antigens, the first step in B-cell activation. CD40L plays a role in costimulation of the B cell by binding to CD40; it does not significantly alter B-cell antigen-receptor binding.

(Choice C) CD18 on neutrophils binds to intercellular adhesion molecule-1 on vascular endothelial cells, allowing the neutrophils to migrate into tissue from the bloodstream. Leukocyte adhesion deficits are usually triggered by mutations to CD18 and marked by recurrent infection. They do not involve CD40L.

(Choice D) The Fc receptor (CD16) on phagocytes binds to IgG attached to microorganisms or cellular debris, leading to opsonophagocytosis. Although IgG levels are very low in hyper-IgM syndrome, which significantly reduces IgG-mediated phagocytosis, the interaction between the phagocyte Fc receptor and antigen-bound antibody remains unaffected.

Educational objective:
CD40-ligand (CD40L) is expressed primarily on activated T cells. It binds to CD40 on antigen-presenting cells, including B cells, leading to their full activation (costimulation). Therefore, CD40L plays a vital role in both the cell-mediated and humoral immune response.

Immunology	Allergy & Immunology	Cell mediated immunity
Subject	System	Topic

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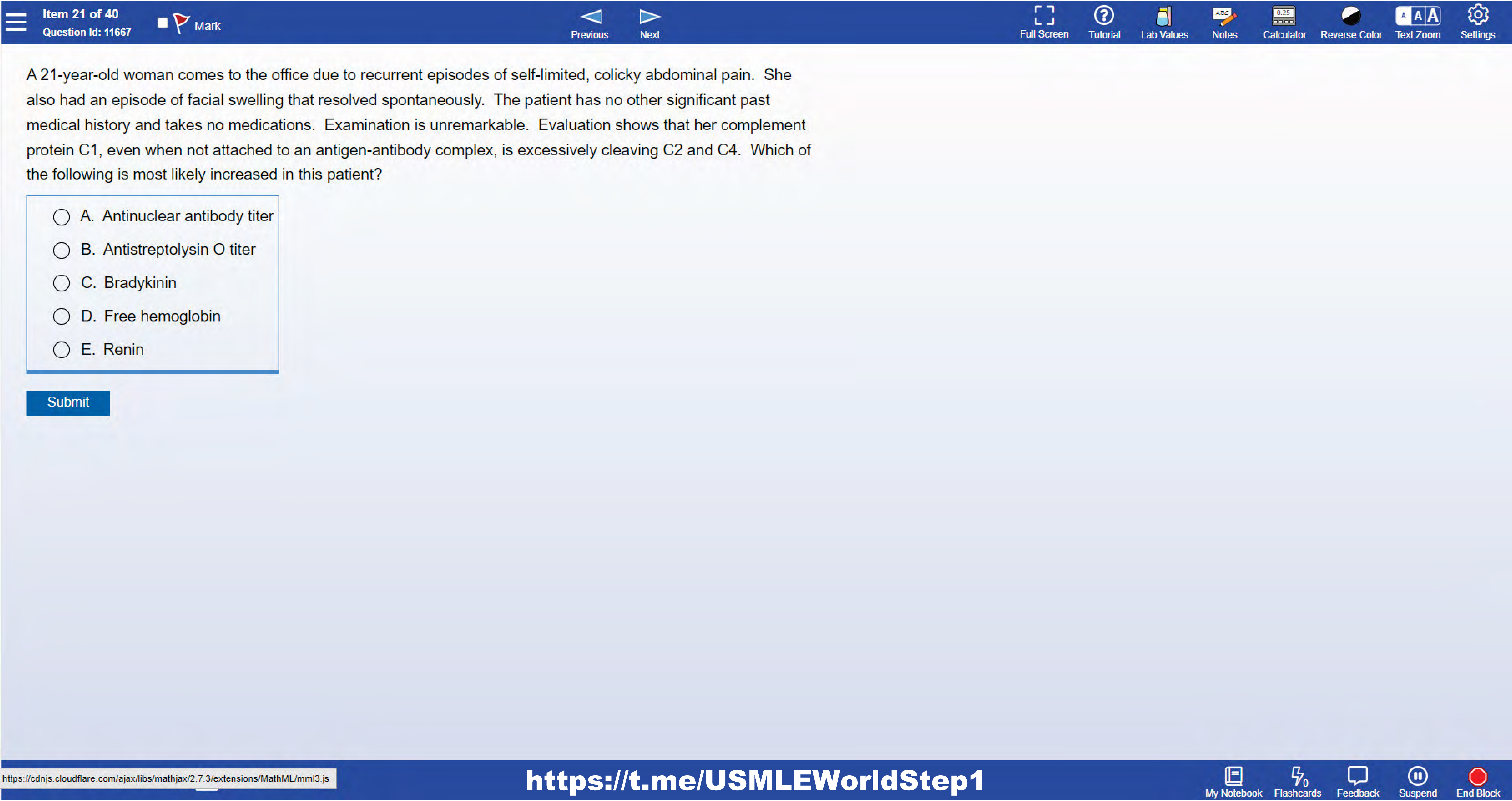
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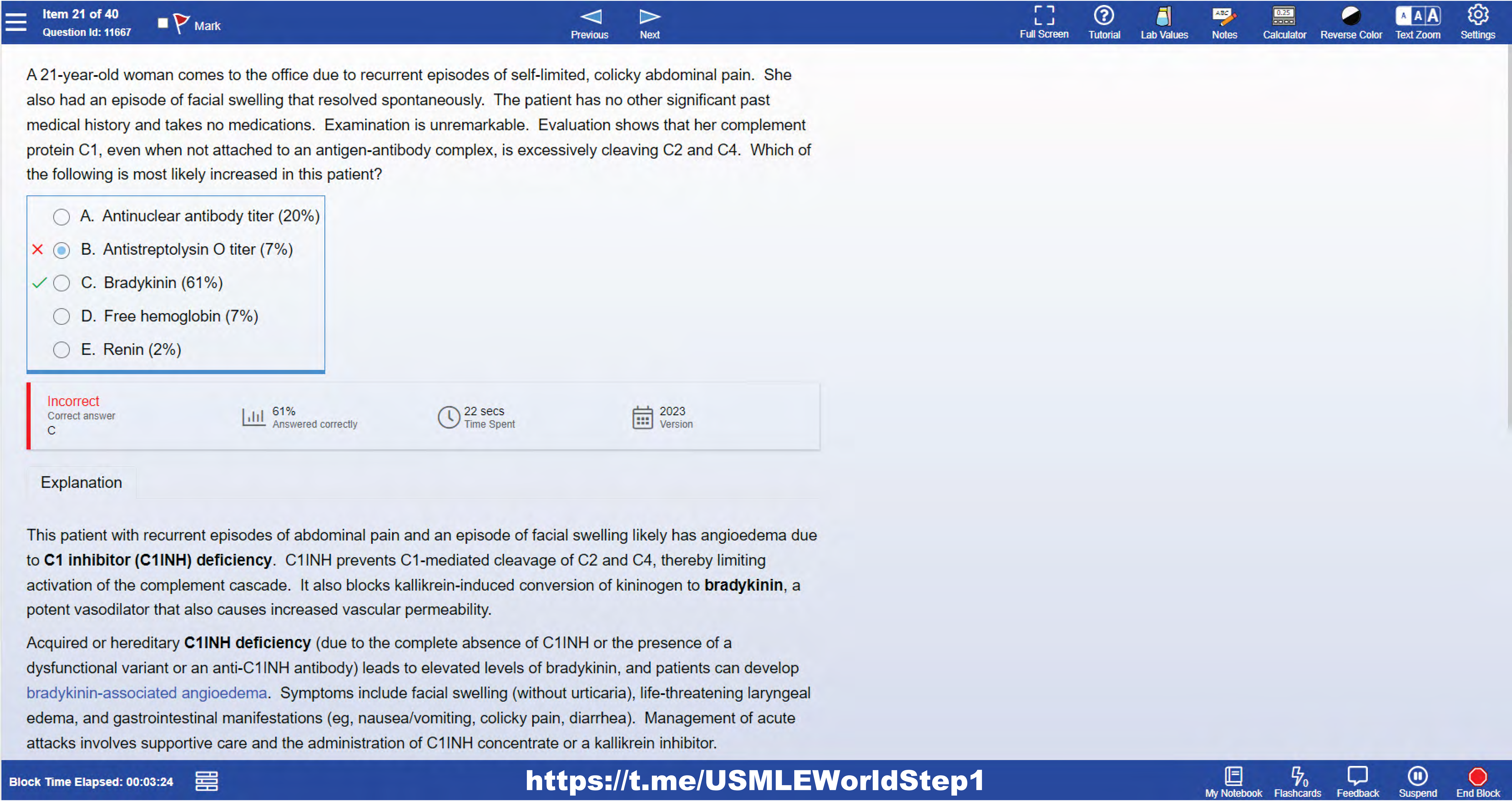
A 21-year-old woman comes to the office due to recurrent episodes of self-limited, colicky abdominal pain. She also had an episode of facial swelling that resolved spontaneously. The patient has no other significant past medical history and takes no medications. Examination is unremarkable. Evaluation shows that her complement protein C1, even when not attached to an antigen-antibody complex, is excessively cleaving C2 and C4. Which of the following is most likely increased in this patient?

○ A. Antinuclear antibody titer
○ B. Antistreptolysin O titer
○ C. Bradykinin
○ D. Free hemoglobin
○ E. Renin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○ A. Antinuclear antibody titer (20%)

✗ ● B. Antistreptolysin O titer (7%)

✓ ○ C. Bradykinin (61%)

○ D. Free hemoglobin (7%)

○ E. Renin (2%)

Incorrect
Correct answer
C

61%
Answered correctly

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Explanation

This patient with recurrent episodes of abdominal pain and an episode of facial swelling likely has angioedema due to **C1 inhibitor (C1INH) deficiency**. C1INH prevents C1-mediated cleavage of C2 and C4, thereby limiting activation of the complement cascade. It also blocks kallikrein-induced conversion of kininogen to **bradykinin**, a potent vasodilator that also causes increased vascular permeability.

Acquired or hereditary **C1INH deficiency** (due to the complete absence of C1INH or the presence of a dysfunctional variant or an anti-C1INH antibody) leads to elevated levels of bradykinin, and patients can develop bradykinin-associated angioedema. Symptoms include facial swelling (without urticaria), life-threatening laryngeal edema, and gastrointestinal manifestations (eg, nausea/vomiting, colicky pain, diarrhea). Management of acute attacks involves supportive care and the administration of C1INH concentrate or a kallikrein inhibitor.

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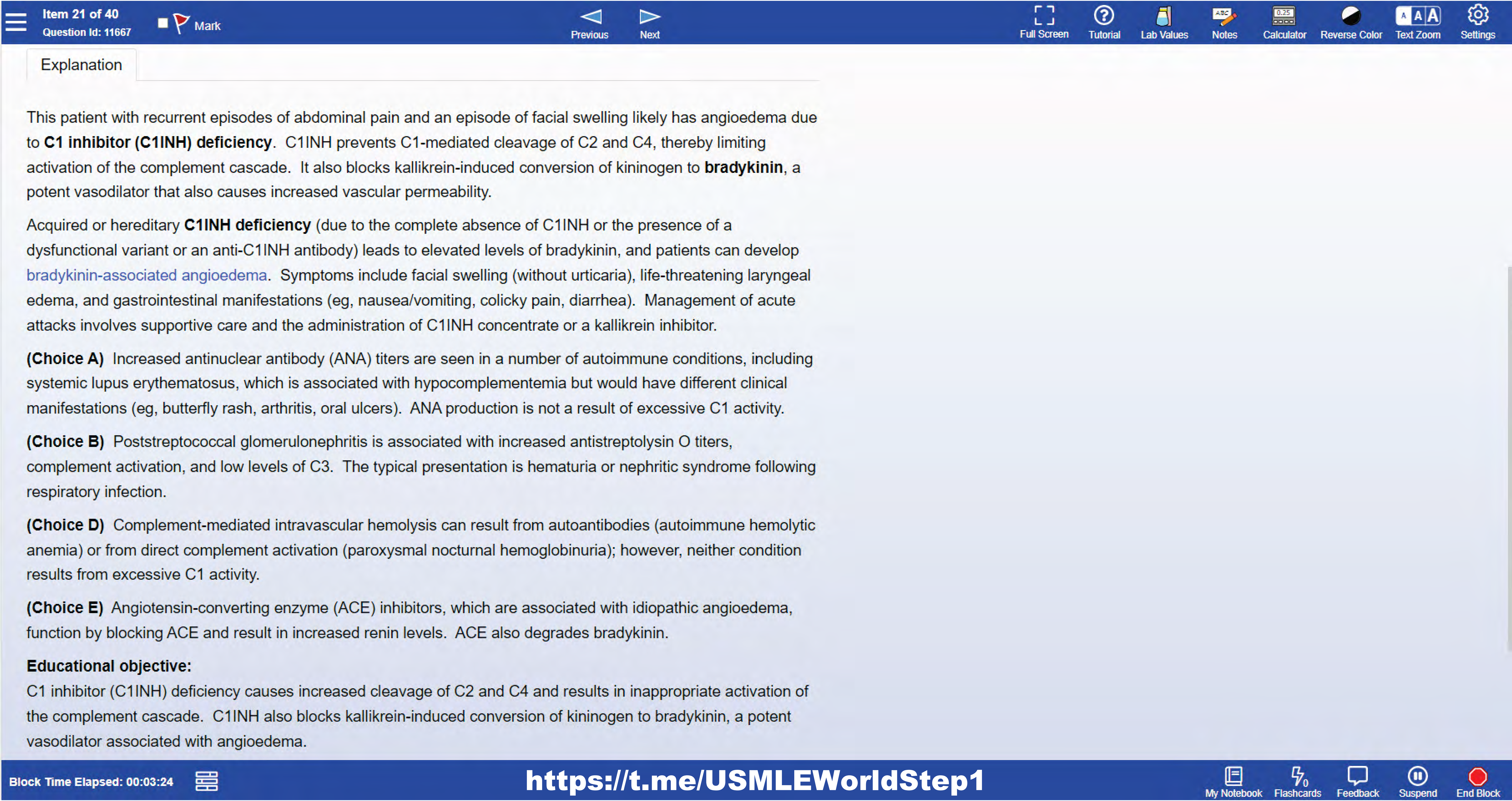

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This patient with recurrent episodes of abdominal pain and an episode of facial swelling likely has angioedema due to **C1 inhibitor (C1INH) deficiency**. C1INH prevents C1-mediated cleavage of C2 and C4, thereby limiting activation of the complement cascade. It also blocks kallikrein-induced conversion of kininogen to **bradykinin**, a potent vasodilator that also causes increased vascular permeability.

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(Choice A) Increased antinuclear antibody (ANA) titers are seen in a number of autoimmune conditions, including systemic lupus erythematosus, which is associated with hypocomplementemia but would have different clinical manifestations (eg, butterfly rash, arthritis, oral ulcers). ANA production is not a result of excessive C1 activity.

(Choice B) Poststreptococcal glomerulonephritis is associated with increased antistreptolysin O titers, complement activation, and low levels of C3. The typical presentation is hematuria or nephritic syndrome following respiratory infection.

(Choice D) Complement-mediated intravascular hemolysis can result from autoantibodies (autoimmune hemolytic anemia) or from direct complement activation (paroxysmal nocturnal hemoglobinuria); however, neither condition results from excessive C1 activity.

(Choice E) Angiotensin-converting enzyme (ACE) inhibitors, which are associated with idiopathic angioedema, function by blocking ACE and result in increased renin levels. ACE also degrades bradykinin.

Educational objective:
C1 inhibitor (C1INH) deficiency causes increased cleavage of C2 and C4 and results in inappropriate activation of the complement cascade. C1INH also blocks kallikrein-induced conversion of kininogen to bradykinin, a potent vasodilator associated with angioedema.

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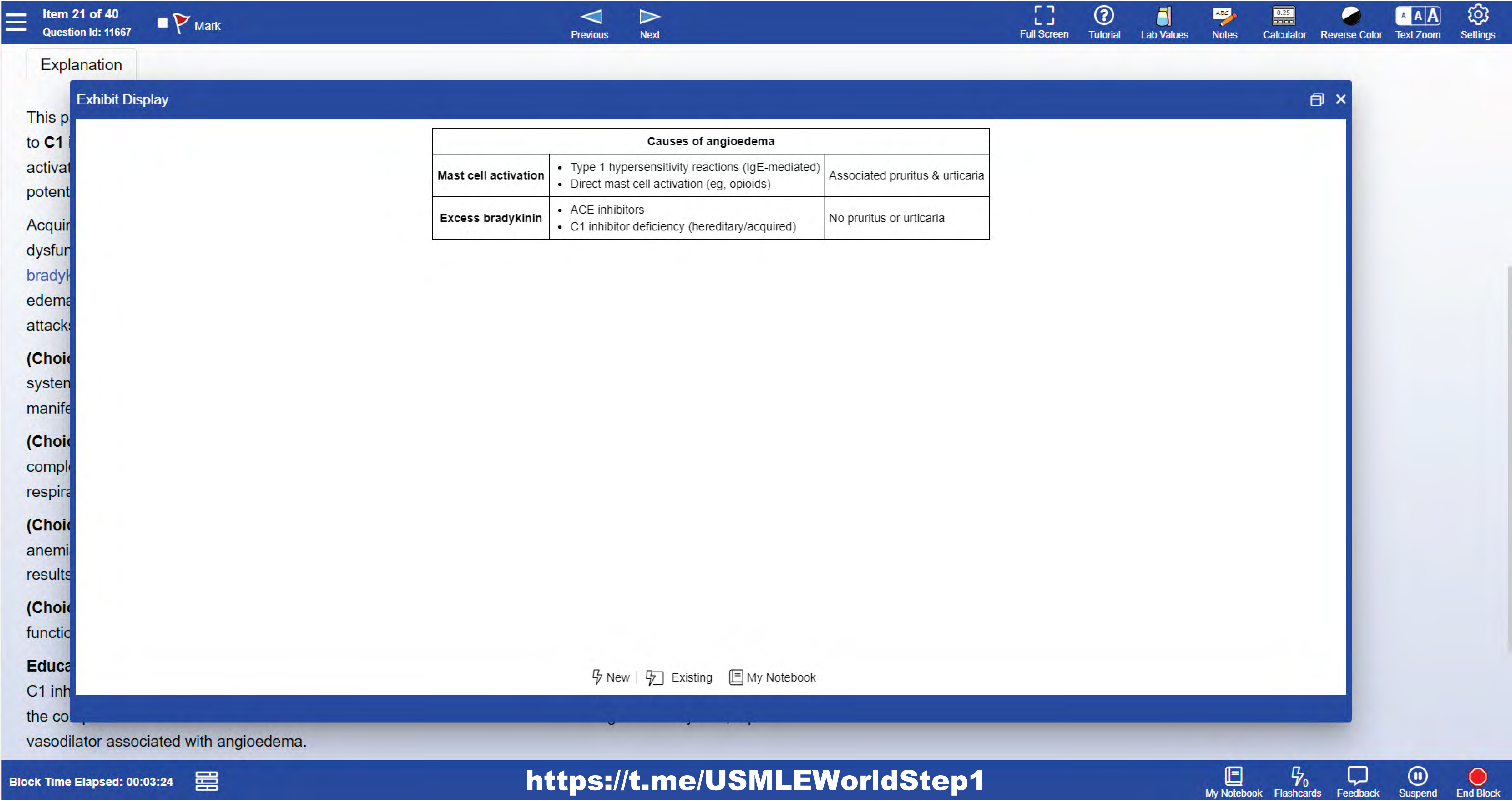
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Causes of angioedema		
Mast cell activation	Type 1 hypersensitivity reactions (IgE-mediated) Direct mast cell activation (eg, opioids)	Associated pruritus & urticaria
Excess bradykinin	ACE inhibitors C1 inhibitor deficiency (hereditary/acquired)	No pruritus or urticaria

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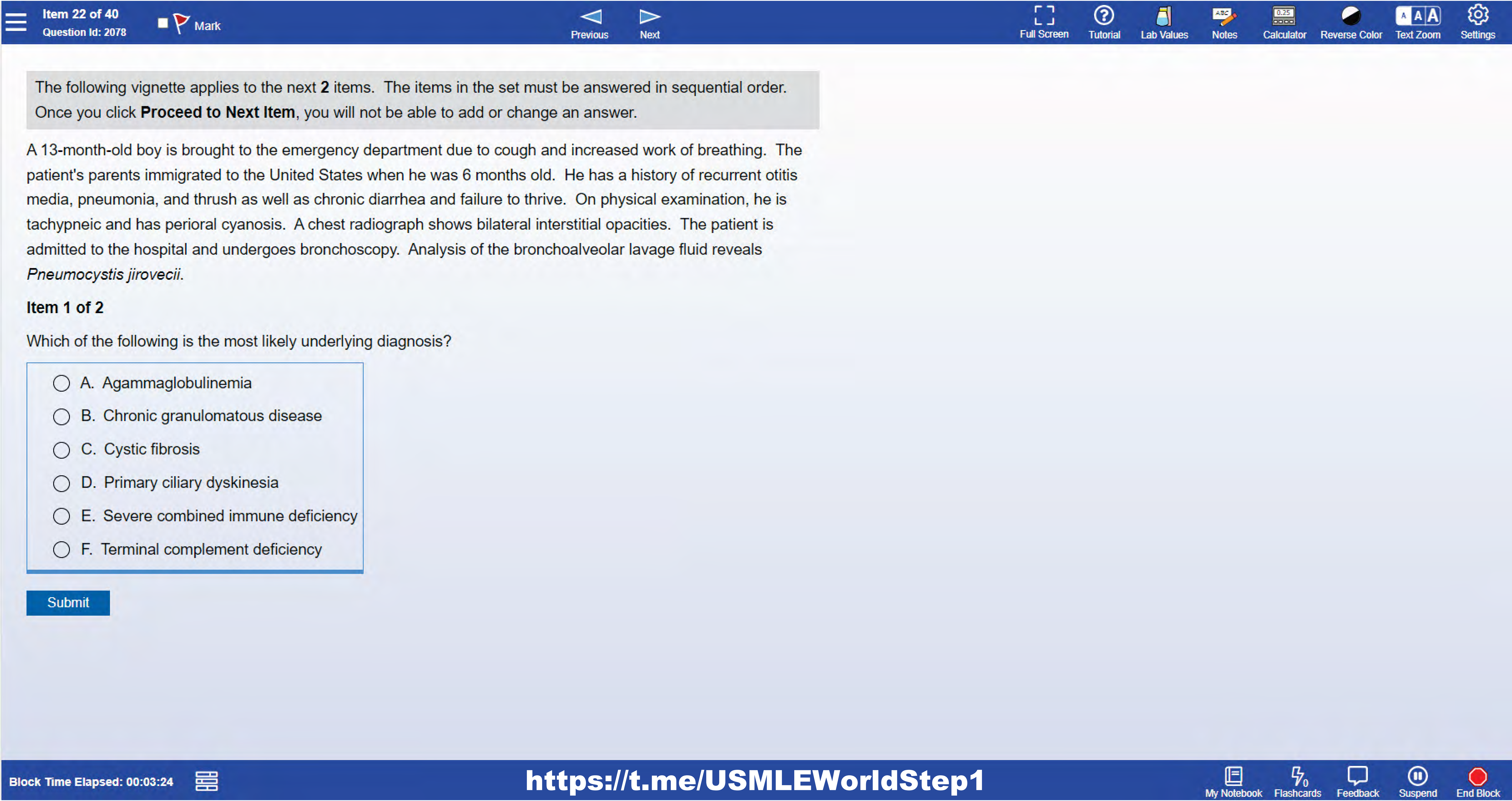
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The following vignette applies to the next **2** items. The items in the set must be answered in sequential order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 13-month-old boy is brought to the emergency department due to cough and increased work of breathing. The patient's parents immigrated to the United States when he was 6 months old. He has a history of recurrent otitis media, pneumonia, and thrush as well as chronic diarrhea and failure to thrive. On physical examination, he is tachypneic and has perioral cyanosis. A chest radiograph shows bilateral interstitial opacities. The patient is admitted to the hospital and undergoes bronchoscopy. Analysis of the bronchoalveolar lavage fluid reveals *Pneumocystis jirovecii*.

Item 1 of 2

Which of the following is the most likely underlying diagnosis?

○ A. Agammaglobulinemia
○ B. Chronic granulomatous disease
○ C. Cystic fibrosis
○ D. Primary ciliary dyskinesia
○ E. Severe combined immune deficiency
○ F. Terminal complement deficiency

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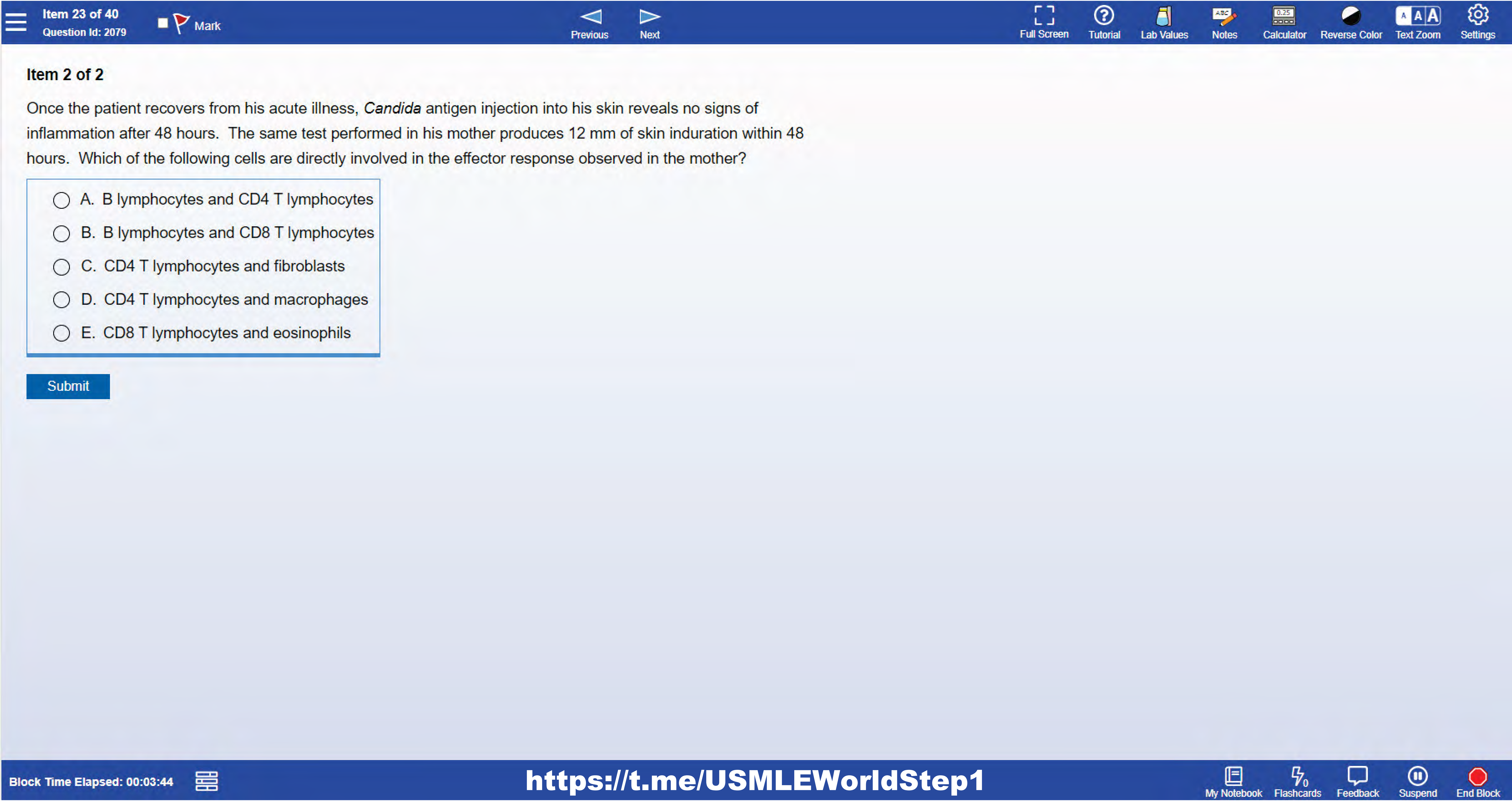
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Item 2 of 2

Once the patient recovers from his acute illness, *Candida* antigen injection into his skin reveals no signs of inflammation after 48 hours. The same test performed in his mother produces 12 mm of skin induration within 48 hours. Which of the following cells are directly involved in the effector response observed in the mother?

○ A. B lymphocytes and CD4 T lymphocytes
○ B. B lymphocytes and CD8 T lymphocytes
○ C. CD4 T lymphocytes and fibroblasts
○ D. CD4 T lymphocytes and macrophages
○ E. CD8 T lymphocytes and eosinophils

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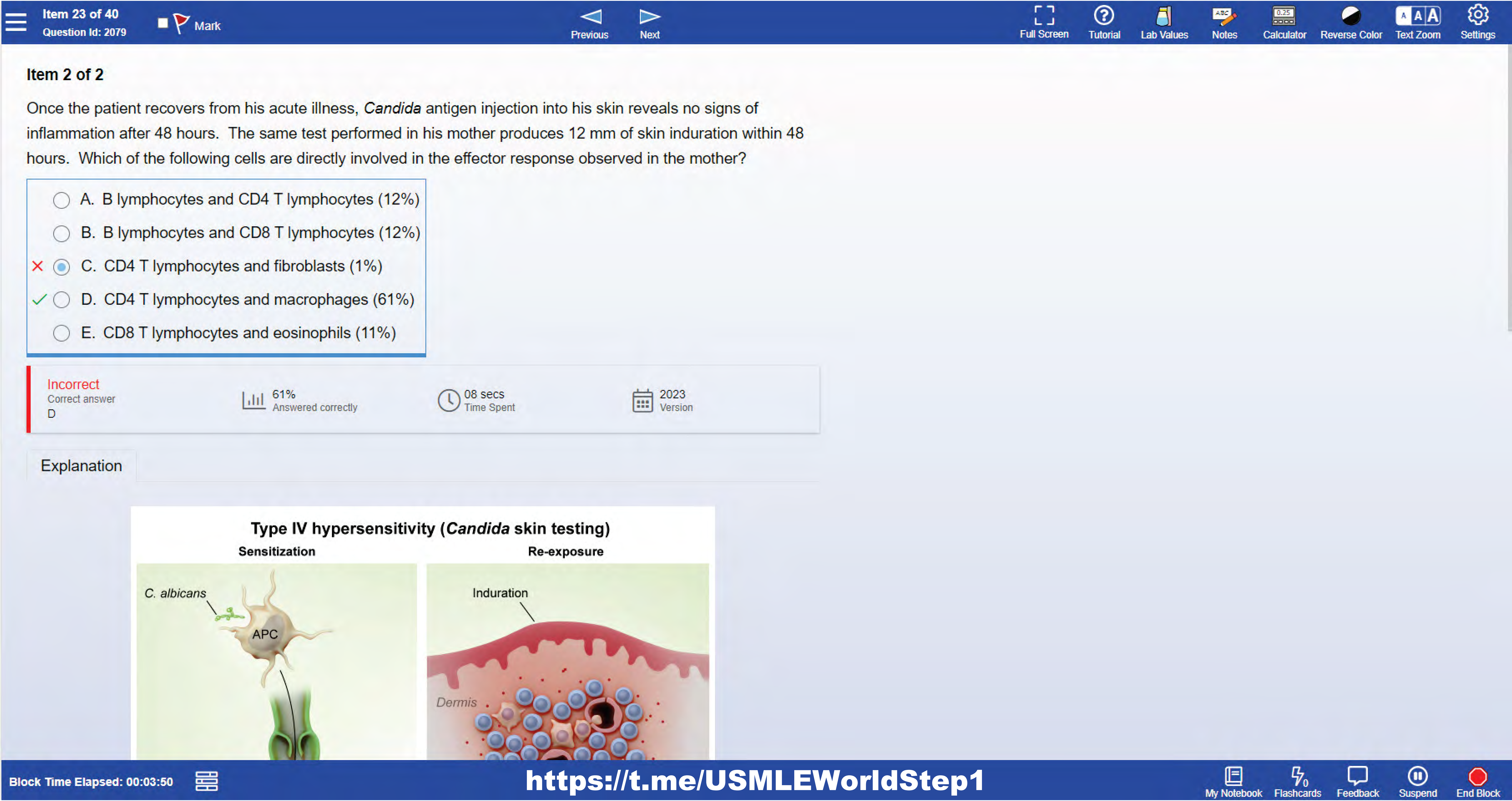
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Question Id: 2079

Item 2 of 2

Once the patient recovers from his acute illness, *Candida* antigen injection into his skin reveals no signs of inflammation after 48 hours. The same test performed in his mother produces 12 mm of skin induration within 48 hours. Which of the following cells are directly involved in the effector response observed in the mother?

○ A. B lymphocytes and CD4 T lymphocytes (12%)

○ B. B lymphocytes and CD8 T lymphocytes (12%)

✗ ● C. CD4 T lymphocytes and fibroblasts (1%)

✓ ○ D. CD4 T lymphocytes and macrophages (61%)

○ E. CD8 T lymphocytes and eosinophils (11%)

Incorrect
Correct answer
D

61%
Answered correctly

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Version

Explanation

Type IV hypersensitivity (*Candida* skin testing)

Sensitization
Re-exposure
C. albicans
APC
Induration
Dermis

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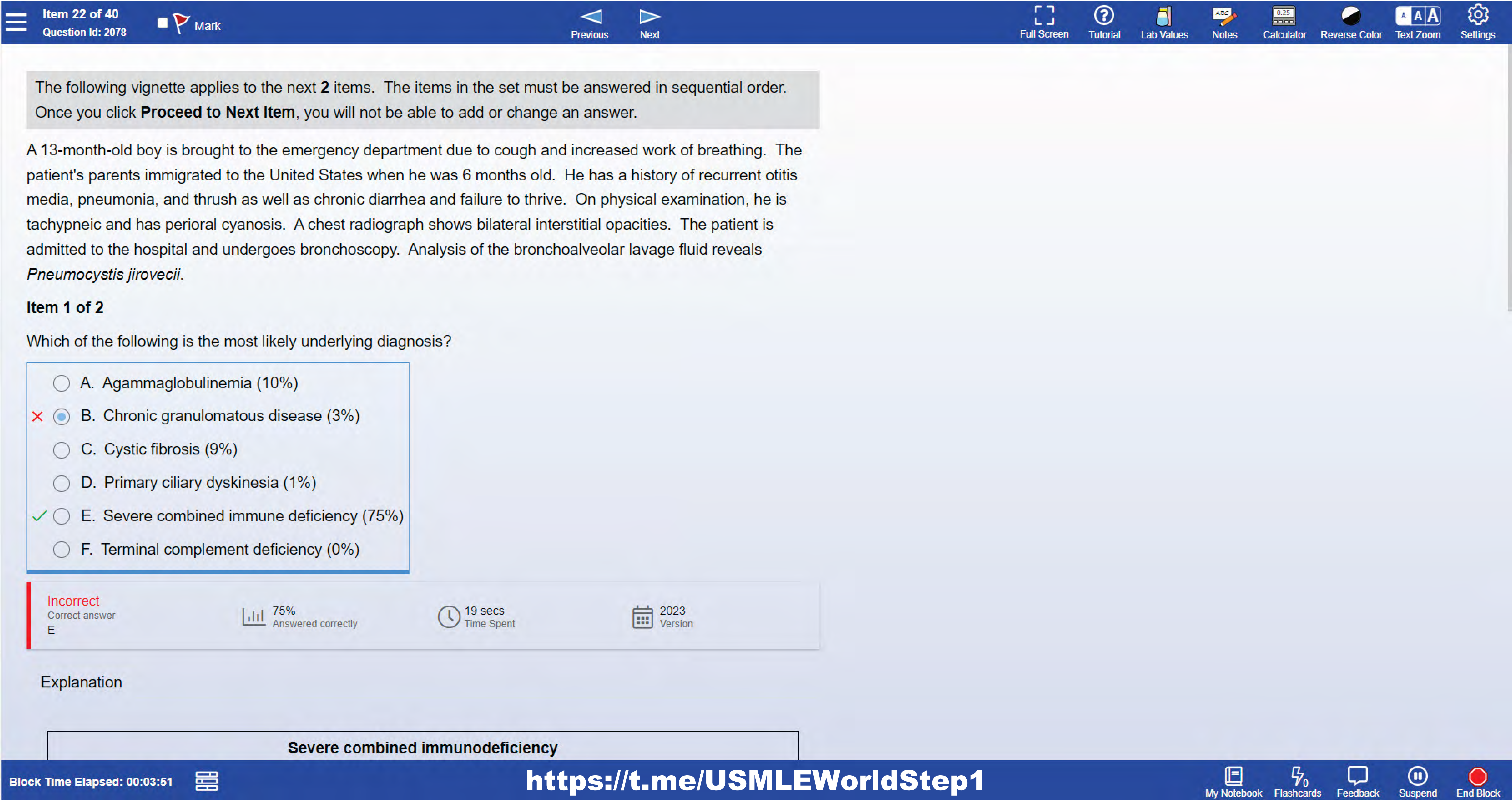
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Item 1 of 2

Which of the following is the most likely underlying diagnosis?

○ A. Agammaglobulinemia (10%)
✗ ● B. Chronic granulomatous disease (3%)
○ C. Cystic fibrosis (9%)
○ D. Primary ciliary dyskinesia (1%)
✓ ○ E. Severe combined immune deficiency (75%)
○ F. Terminal complement deficiency (0%)

Incorrect
Correct answer
E

75%
Answered correctly

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Explanation

Severe combined immunodeficiency

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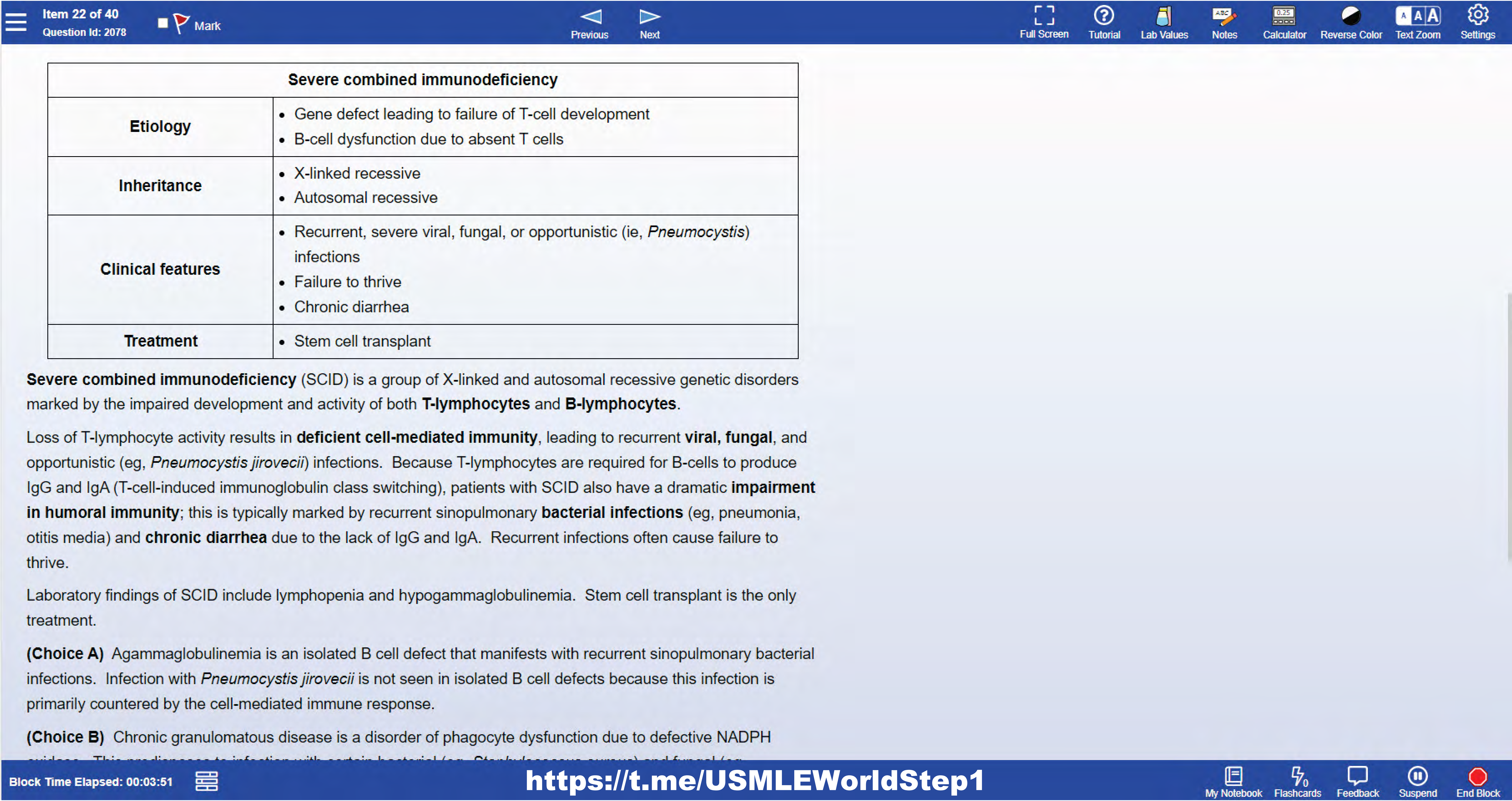
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Severe combined immunodeficiency	
Etiology	• Gene defect leading to failure of T-cell development • B-cell dysfunction due to absent T cells
Inheritance	• X-linked recessive • Autosomal recessive
Clinical features	• Recurrent, severe viral, fungal, or opportunistic (ie, *Pneumocystis*) infections • Failure to thrive • Chronic diarrhea
Treatment	• Stem cell transplant

Severe combined immunodeficiency (SCID) is a group of X-linked and autosomal recessive genetic disorders marked by the impaired development and activity of both **T-lymphocytes** and **B-lymphocytes**.

Loss of T-lymphocyte activity results in **deficient cell-mediated immunity**, leading to recurrent **viral, fungal**, and opportunistic (eg, *Pneumocystis jirovecii*) infections. Because T-lymphocytes are required for B-cells to produce IgG and IgA (T-cell-induced immunoglobulin class switching), patients with SCID also have a dramatic **impairment in humoral immunity**; this is typically marked by recurrent sinopulmonary **bacterial infections** (eg, pneumonia, otitis media) and **chronic diarrhea** due to the lack of IgG and IgA. Recurrent infections often cause failure to thrive.

Laboratory findings of SCID include lymphopenia and hypogammaglobulinemia. Stem cell transplant is the only treatment.

(Choice A) Agammaglobulinemia is an isolated B cell defect that manifests with recurrent sinopulmonary bacterial infections. Infection with *Pneumocystis jirovecii* is not seen in isolated B cell defects because this infection is primarily countered by the cell-mediated immune response.

(Choice B) Chronic granulomatous disease is a disorder of phagocyte dysfunction due to defective NADPH

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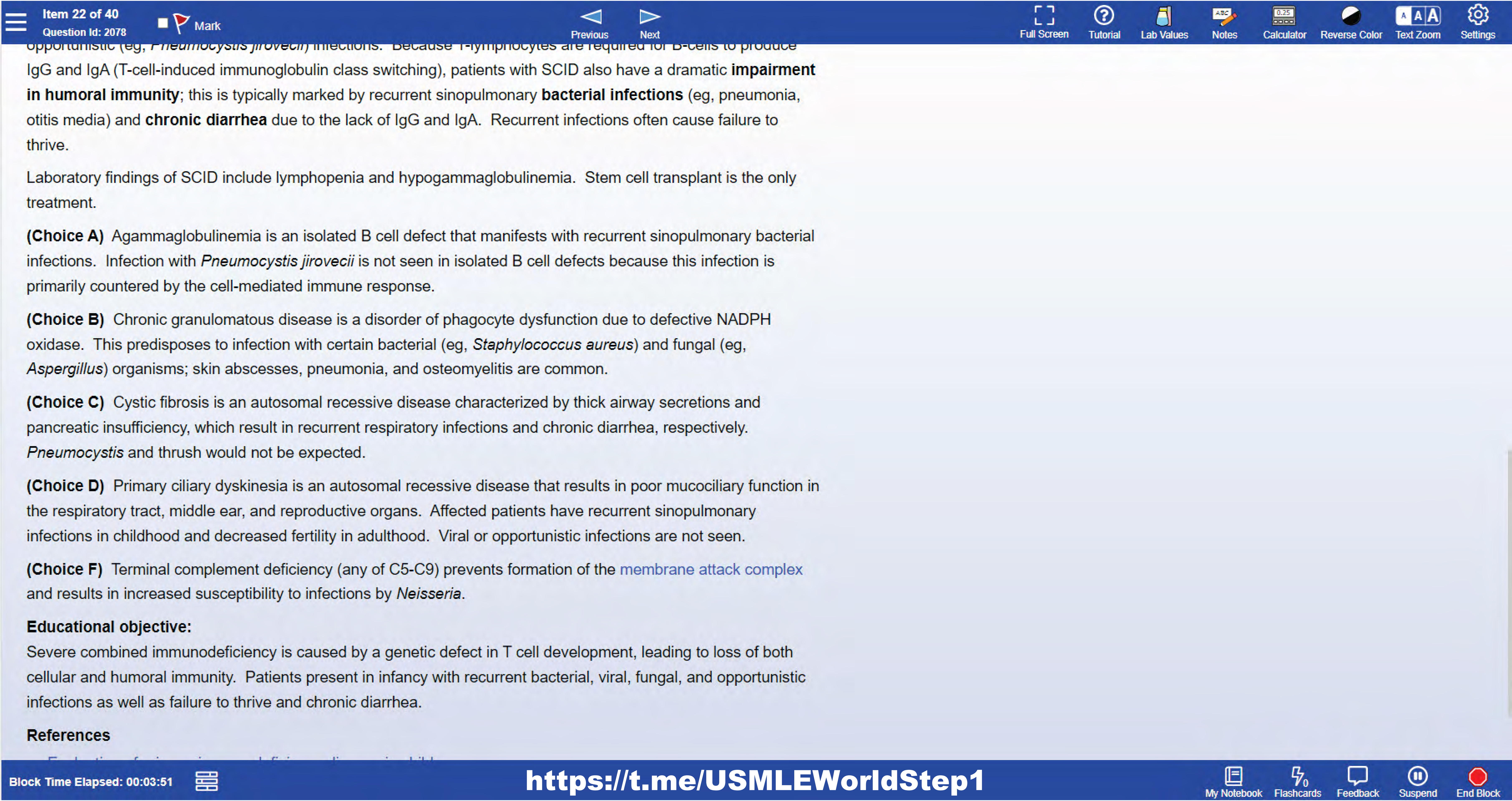


opportunistic (eg, *Pneumocystis jirovecii*) infections. Because T-lymphocytes are required for B-cells to produce IgG and IgA (T-cell-induced immunoglobulin class switching), patients with SCID also have a dramatic **impairment in humoral immunity**; this is typically marked by recurrent sinopulmonary **bacterial infections** (eg, pneumonia, otitis media) and **chronic diarrhea** due to the lack of IgG and IgA. Recurrent infections often cause failure to thrive.

Laboratory findings of SCID include lymphopenia and hypogammaglobulinemia. Stem cell transplant is the only treatment.

(Choice A) Agammaglobulinemia is an isolated B cell defect that manifests with recurrent sinopulmonary bacterial infections. Infection with *Pneumocystis jirovecii* is not seen in isolated B cell defects because this infection is primarily countered by the cell-mediated immune response.

(Choice B) Chronic granulomatous disease is a disorder of phagocyte dysfunction due to defective NADPH oxidase. This predisposes to infection with certain bacterial (eg, *Staphylococcus aureus*) and fungal (eg, *Aspergillus*) organisms; skin abscesses, pneumonia, and osteomyelitis are common.

(Choice C) Cystic fibrosis is an autosomal recessive disease characterized by thick airway secretions and pancreatic insufficiency, which result in recurrent respiratory infections and chronic diarrhea, respectively. *Pneumocystis* and thrush would not be expected.

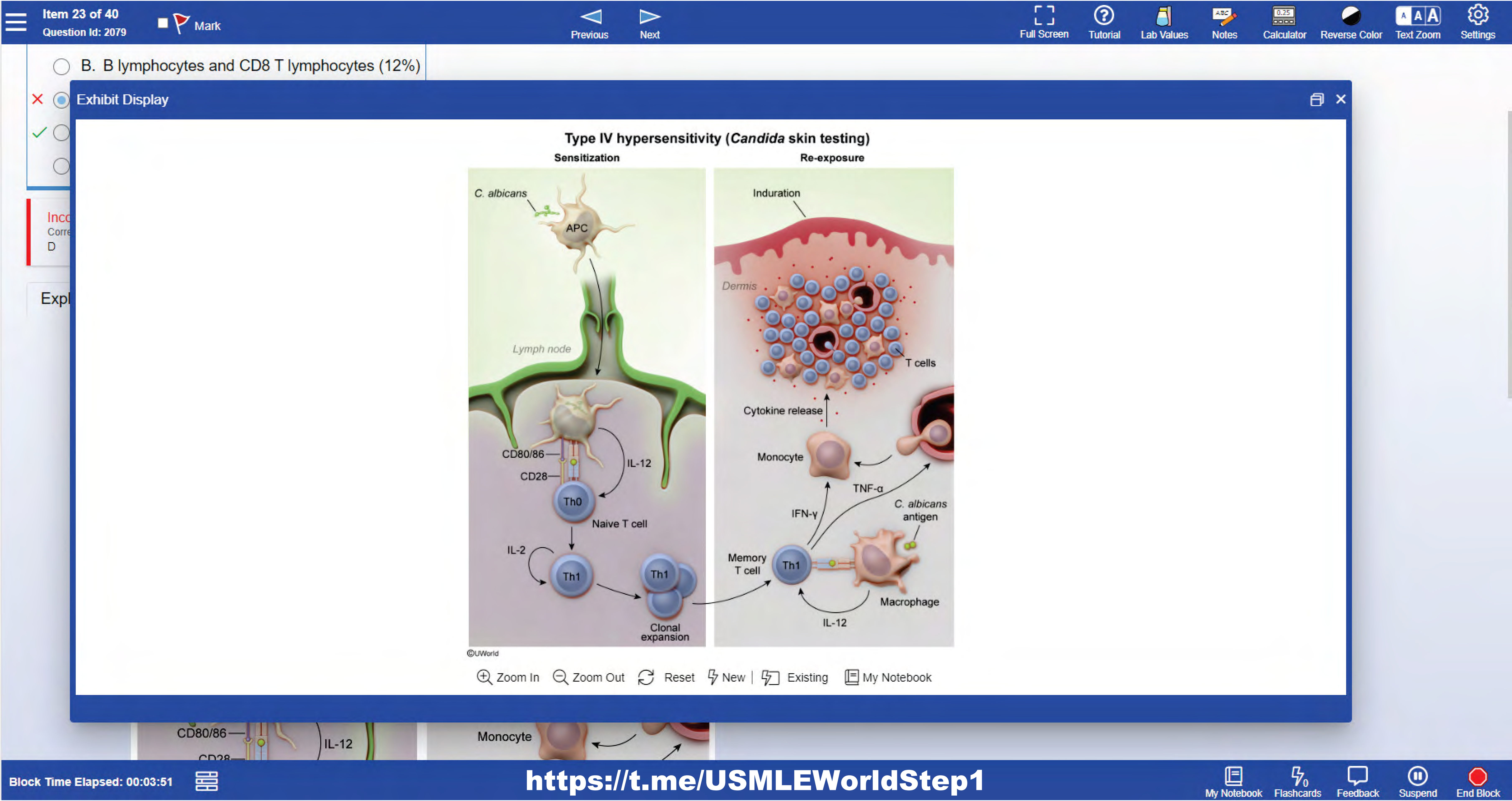
(Choice D) Primary ciliary dyskinesia is an autosomal recessive disease that results in poor mucociliary function in the respiratory tract, middle ear, and reproductive organs. Affected patients have recurrent sinopulmonary infections in childhood and decreased fertility in adulthood. Viral or opportunistic infections are not seen.

(Choice F) Terminal complement deficiency (any of C5-C9) prevents formation of the membrane attack complex and results in increased susceptibility to infections by *Neisseria*.

Educational objective:

Severe combined immunodeficiency is caused by a genetic defect in T cell development, leading to loss of both cellular and humoral immunity. Patients present in infancy with recurrent bacterial, viral, fungal, and opportunistic infections as well as failure to thrive and chronic diarrhea.

References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Sensitization
Re-exposure
C. albicans
APC
Lymph node
CD80/86
CD28
IL-12
Th0
Naive T cell
IL-2
Th1
Th1
Clonal expansion
Induration
Dermis
T cells
Cytokine release
Monocyte
TNF-α
IFN-γ
C. albicans antigen
Memory T cell
Th1
Macrophage
IL-12
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○ B. B lymphocytes and CD8 T lymphocytes (12%)

Type IV hypersensitivity (*Candida* skin testing)

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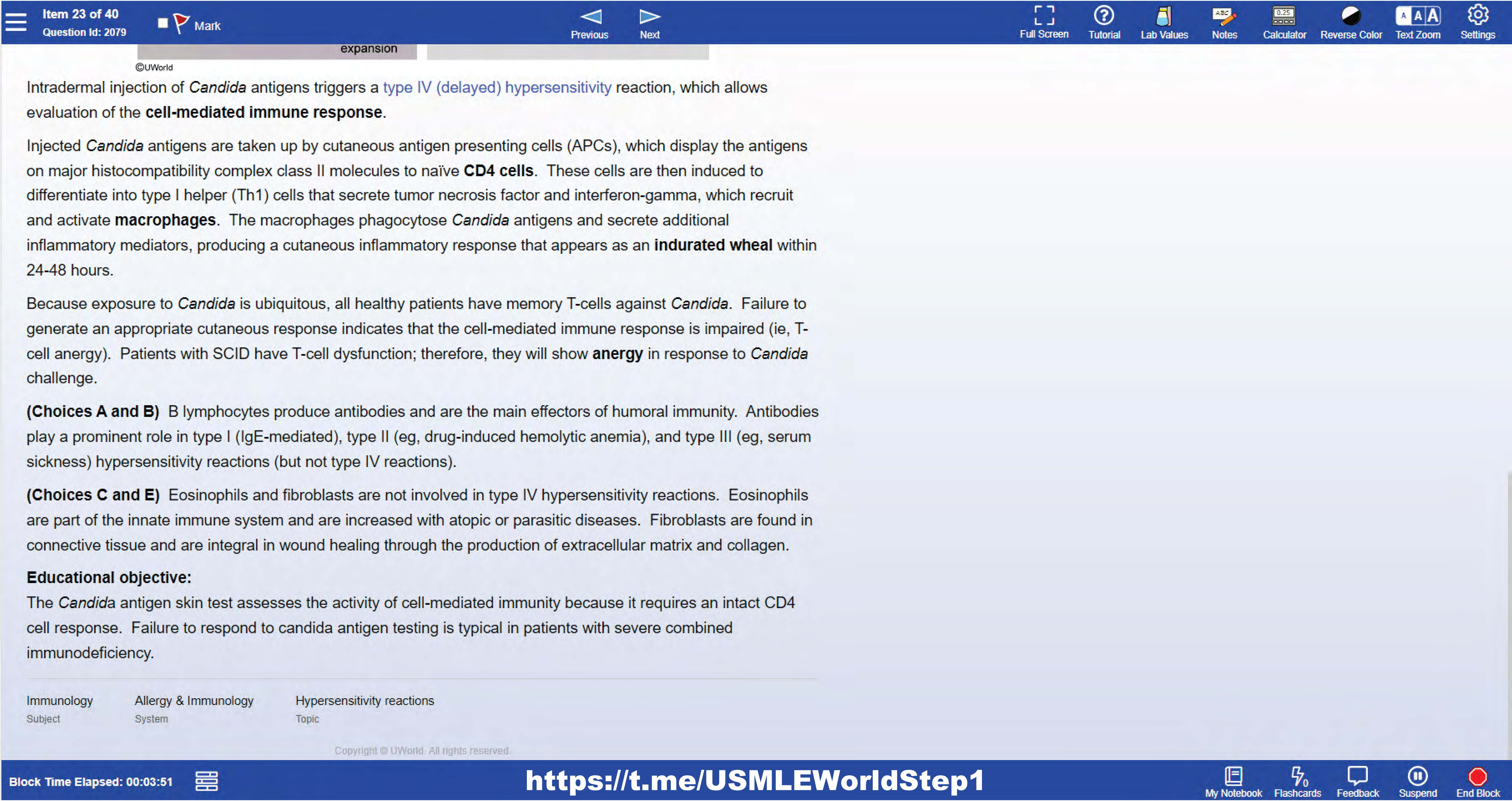

Intradermal injection of *Candida* antigens triggers a type IV (delayed) hypersensitivity reaction, which allows evaluation of the **cell-mediated immune response**.

Injected *Candida* antigens are taken up by cutaneous antigen presenting cells (APCs), which display the antigens on major histocompatibility complex class II molecules to naïve **CD4 cells**. These cells are then induced to differentiate into type I helper (Th1) cells that secrete tumor necrosis factor and interferon-gamma, which recruit and activate **macrophages**. The macrophages phagocytose *Candida* antigens and secrete additional inflammatory mediators, producing a cutaneous inflammatory response that appears as an **indurated wheal** within 24-48 hours.

Because exposure to *Candida* is ubiquitous, all healthy patients have memory T-cells against *Candida*. Failure to generate an appropriate cutaneous response indicates that the cell-mediated immune response is impaired (ie, T-cell anergy). Patients with SCID have T-cell dysfunction; therefore, they will show **anergy** in response to *Candida* challenge.

(Choices A and B) B lymphocytes produce antibodies and are the main effectors of humoral immunity. Antibodies play a prominent role in type I (IgE-mediated), type II (eg, drug-induced hemolytic anemia), and type III (eg, serum sickness) hypersensitivity reactions (but not type IV reactions).

(Choices C and E) Eosinophils and fibroblasts are not involved in type IV hypersensitivity reactions. Eosinophils are part of the innate immune system and are increased with atopic or parasitic diseases. Fibroblasts are found in connective tissue and are integral in wound healing through the production of extracellular matrix and collagen.

Educational objective:
The *Candida* antigen skin test assesses the activity of cell-mediated immunity because it requires an intact CD4 cell response. Failure to respond to candida antigen testing is typical in patients with severe combined immunodeficiency.

Immunology	Allergy & Immunology	Hypersensitivity reactions
Subject	System	Topic

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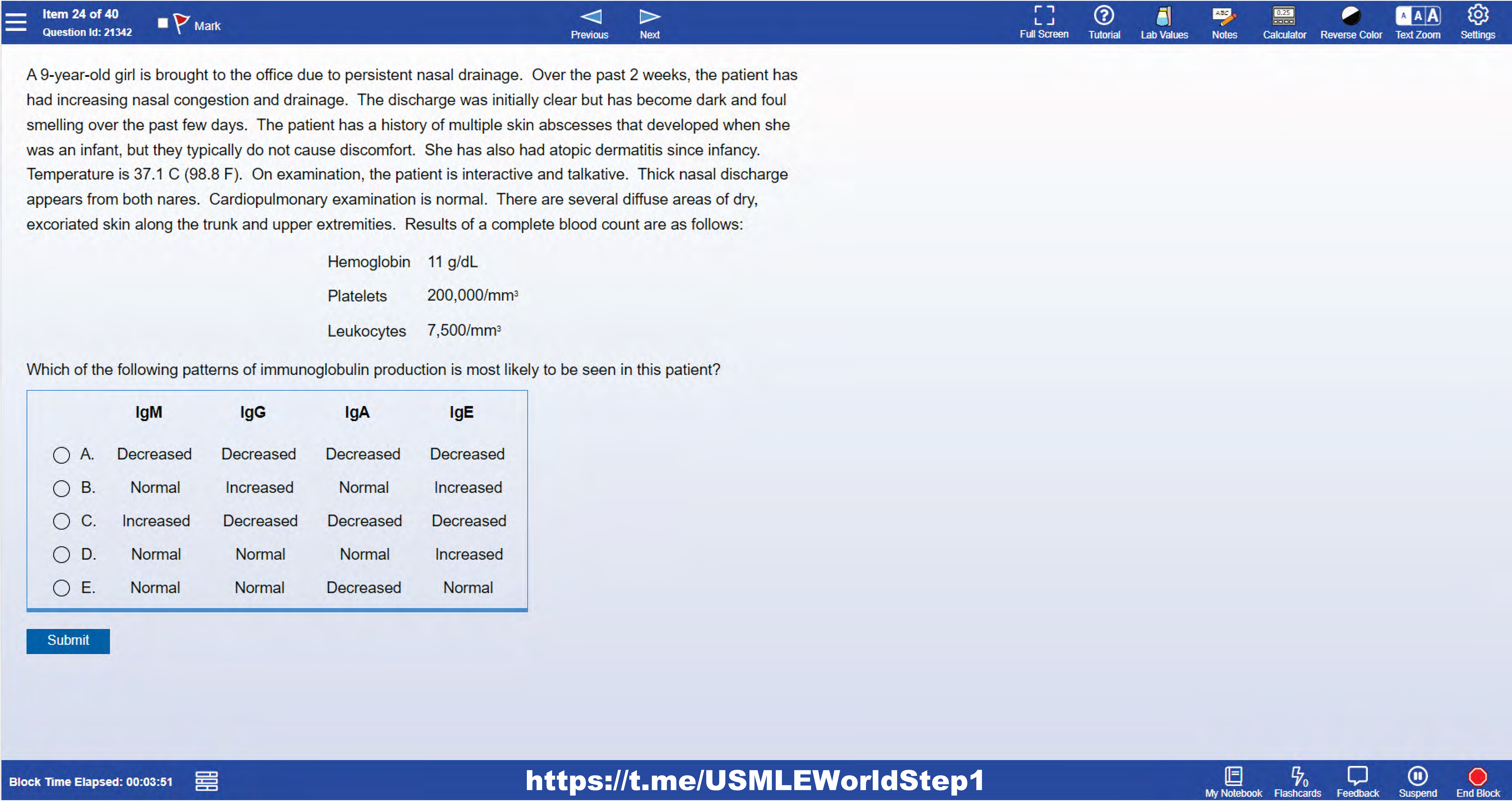
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A 9-year-old girl is brought to the office due to persistent nasal drainage. Over the past 2 weeks, the patient has had increasing nasal congestion and drainage. The discharge was initially clear but has become dark and foul smelling over the past few days. The patient has a history of multiple skin abscesses that developed when she was an infant, but they typically do not cause discomfort. She has also had atopic dermatitis since infancy. Temperature is 37.1 C (98.8 F). On examination, the patient is interactive and talkative. Thick nasal discharge appears from both nares. Cardiopulmonary examination is normal. There are several diffuse areas of dry, excoriated skin along the trunk and upper extremities. Results of a complete blood count are as follows:

Hemoglobin	11 g/dL
Platelets	200,000/mm^3
Leukocytes	7,500/mm^3

Which of the following patterns of immunoglobulin production is most likely to be seen in this patient?

		IgM	IgG	IgA	IgE
○	A.	Decreased	Decreased	Decreased	Decreased
○	B.	Normal	Increased	Normal	Increased
○	C.	Increased	Decreased	Decreased	Decreased
○	D.	Normal	Normal	Normal	Increased
○	E.	Normal	Normal	Decreased	Normal

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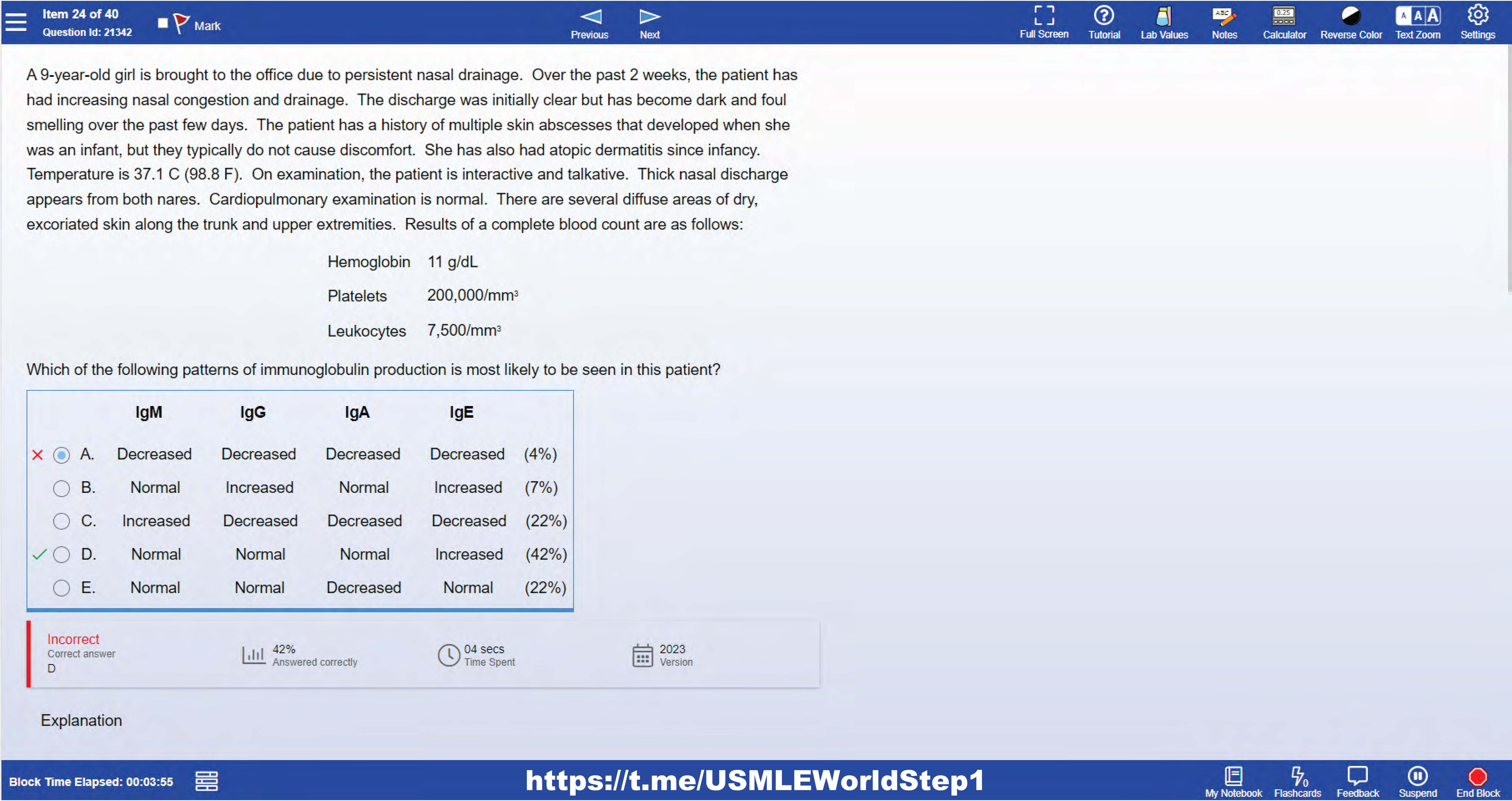
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Hemoglobin	11 g/dL
Platelets	200,000/mm^3
Leukocytes	7,500/mm^3

Which of the following patterns of immunoglobulin production is most likely to be seen in this patient?

		IgM	IgG	IgA	IgE	
✗ ●	A.	Decreased	Decreased	Decreased	Decreased	(4%)
○	B.	Normal	Increased	Normal	Increased	(7%)
○	C.	Increased	Decreased	Decreased	Decreased	(22%)
✓ ○	D.	Normal	Normal	Normal	Increased	(42%)
○	E.	Normal	Normal	Decreased	Normal	(22%)

Incorrect
Correct answer
D

42%
Answered correctly

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Explanation

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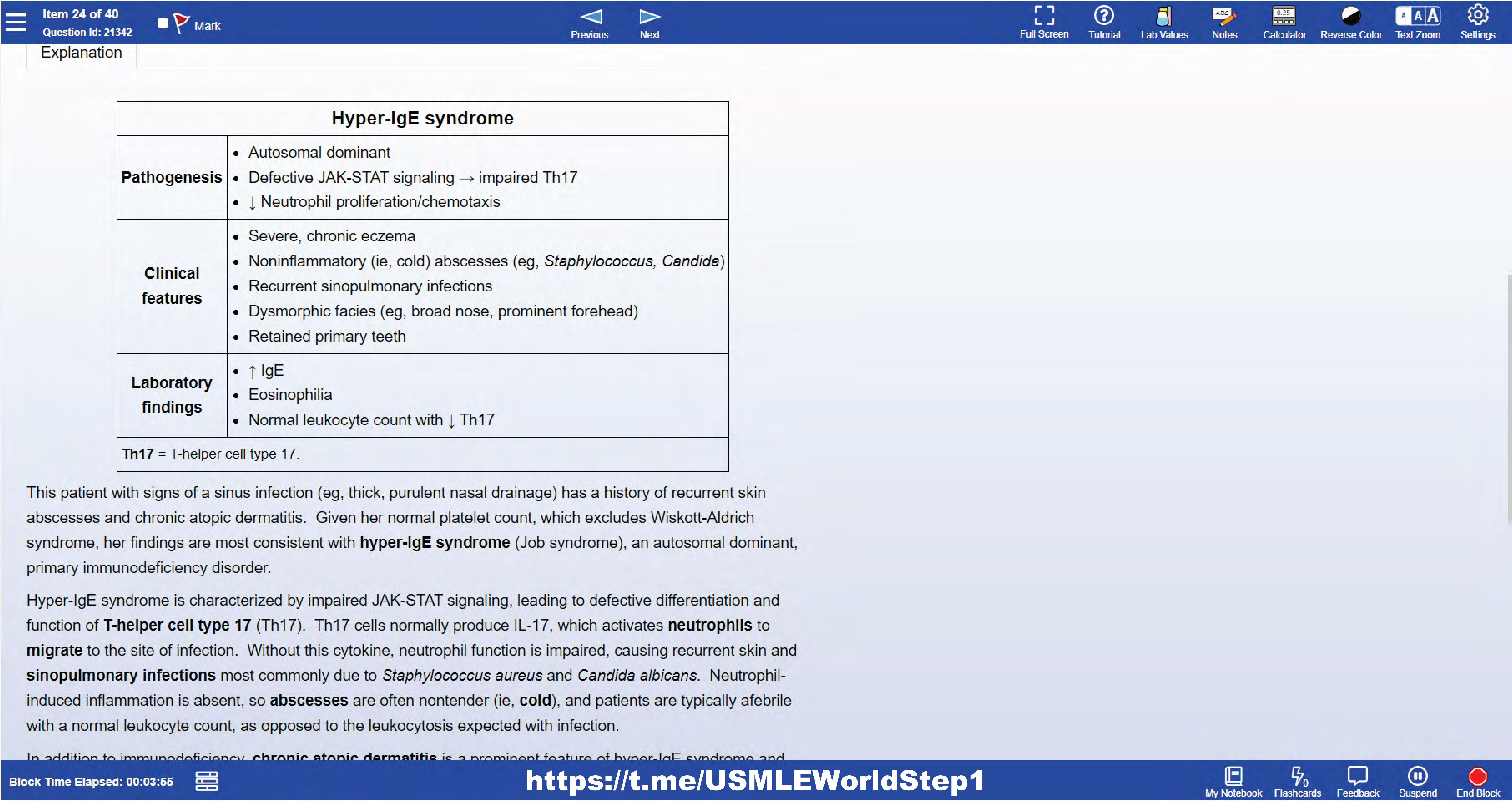
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Explanation

Hyper-IgE syndrome	
Pathogenesis	- Autosomal dominant - Defective JAK-STAT signaling → impaired Th17 - ↓ Neutrophil proliferation/chemotaxis
Clinical features	- Severe, chronic eczema - Noninflammatory (ie, cold) abscesses (eg, *Staphylococcus, Candida*) - Recurrent sinopulmonary infections - Dysmorphic facies (eg, broad nose, prominent forehead) - Retained primary teeth
Laboratory findings	- ↑ IgE - Eosinophilia - Normal leukocyte count with ↓ Th17
Th17 = T-helper cell type 17.	

This patient with signs of a sinus infection (eg, thick, purulent nasal drainage) has a history of recurrent skin abscesses and chronic atopic dermatitis. Given her normal platelet count, which excludes Wiskott-Aldrich syndrome, her findings are most consistent with **hyper-IgE syndrome** (Job syndrome), an autosomal dominant, primary immunodeficiency disorder.

Hyper-IgE syndrome is characterized by impaired JAK-STAT signaling, leading to defective differentiation and function of **T-helper cell type 17** (Th17). Th17 cells normally produce IL-17, which activates **neutrophils** to **migrate** to the site of infection. Without this cytokine, neutrophil function is impaired, causing recurrent skin and **sinopulmonary infections** most commonly due to *Staphylococcus aureus* and *Candida albicans*. Neutrophil-induced inflammation is absent, so **abscesses** are often nontender (ie, **cold**), and patients are typically afebrile with a normal leukocyte count, as opposed to the leukocytosis expected with infection.

In addition to immunodeficiency, **chronic atopic dermatitis** is a prominent feature of hyper-IgE syndrome and

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migrate to the site of infection. Without this cytokine, neutrophil function is impaired, causing recurrent skin and **sinopulmonary infections** most commonly due to *Staphylococcus aureus* and *Candida albicans*. Neutrophil-induced inflammation is absent, so **abscesses** are often nontender (ie, **cold**), and patients are typically afebrile with a normal leukocyte count, as opposed to the leukocytosis expected with infection.

In addition to immunodeficiency, **chronic atopic dermatitis** is a prominent feature of hyper-IgE syndrome and typically begins in early infancy. Colonization of *S aureus* and *C albicans* on the skin triggers mast cell histamine release, causing severe pruritus and an eczematous rash. Patients characteristically have **eosinophilia** and **elevated IgE** related to the dermatitis, but **other immunoglobulin levels** are usually **normal**. A low Th17 count supports the diagnosis, and molecular genetic testing is confirmatory.

(Choice A) All immunoglobulin levels are decreased/absent in X-linked agammaglobulinemia due to impaired B-cell maturation. Severe sinopulmonary and invasive bacterial infections begin in infancy, and failure to thrive is typical. Without immunoglobulin replacement most children will have near fatal infections early in life.

(Choice B) Chronic eczema without an underlying immunodeficiency can cause elevated IgE, and IgG may also be high if the rash is superinfected. However, the affected area would be erythematous and tender, unlike this patient's cold abscess, making isolated atopic disease unlikely.

(Choice C) Hyper-IgM syndrome, in which immunoglobulin class-switching is impaired due to CD40 ligand deficiency, typically presents in infancy with sinopulmonary and opportunistic infections. Recurrent cold skin abscesses do not typically occur.

(Choice E) Selective IgA deficiency can cause recurrent sinopulmonary infections and is associated with an increased risk for atopy. However, skin infections would not be expected.

Educational objective:

Hyper-IgE syndrome is characterized by elevated IgE levels and is caused by impaired neutrophil activation and migration due to a defect in T-helper cell type 17 cells. Typical findings include noninflammatory (ie, cold) abscesses, recurrent sinopulmonary infections, and chronic atopic dermatitis.

References

- Hyper IgE syndromes: clinical and molecular characteristics.

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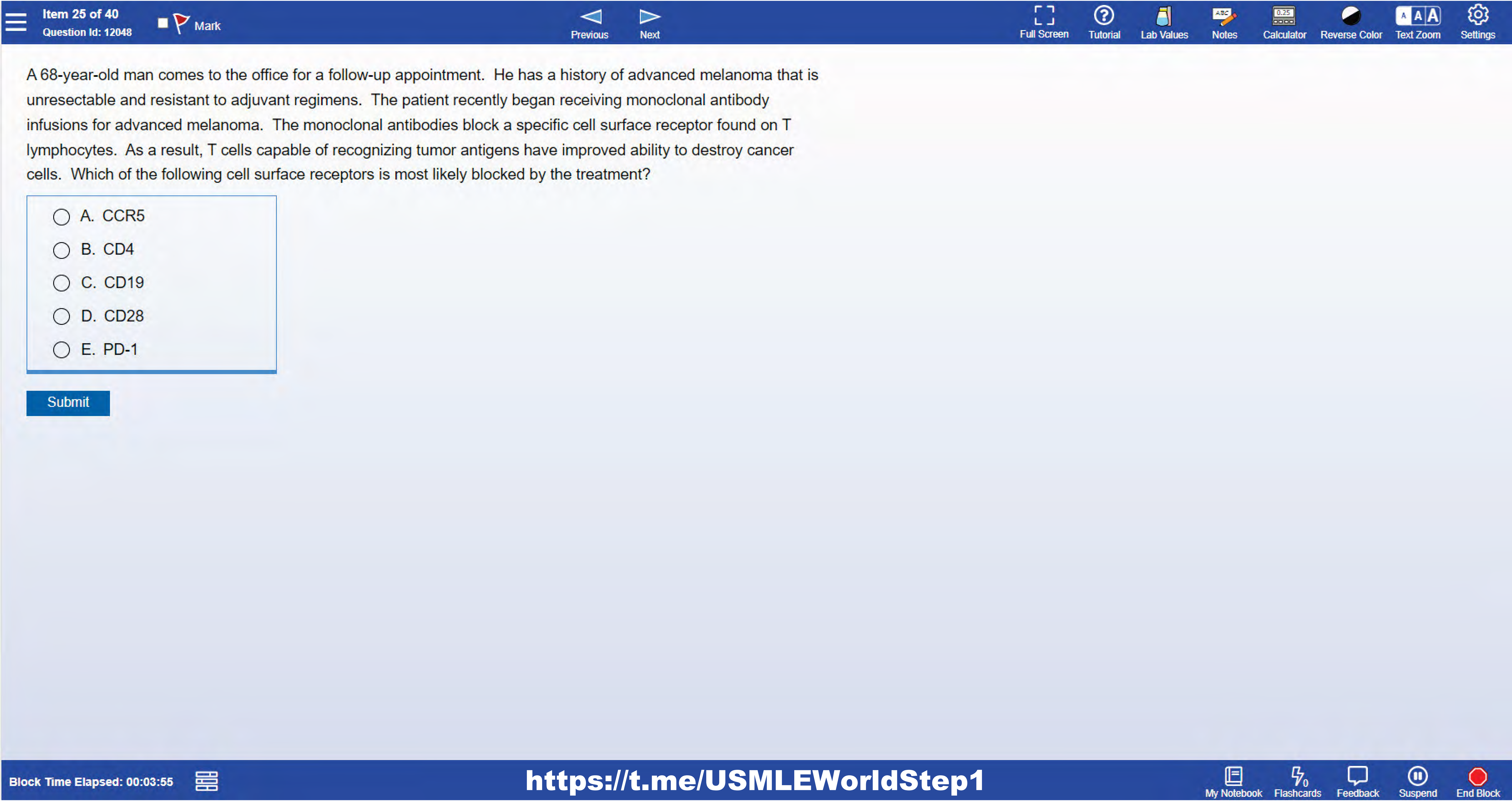
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A 68-year-old man comes to the office for a follow-up appointment. He has a history of advanced melanoma that is unresectable and resistant to adjuvant regimens. The patient recently began receiving monoclonal antibody infusions for advanced melanoma. The monoclonal antibodies block a specific cell surface receptor found on T lymphocytes. As a result, T cells capable of recognizing tumor antigens have improved ability to destroy cancer cells. Which of the following cell surface receptors is most likely blocked by the treatment?

○ A. CCR5
○ B. CD4
○ C. CD19
○ D. CD28
○ E. PD-1

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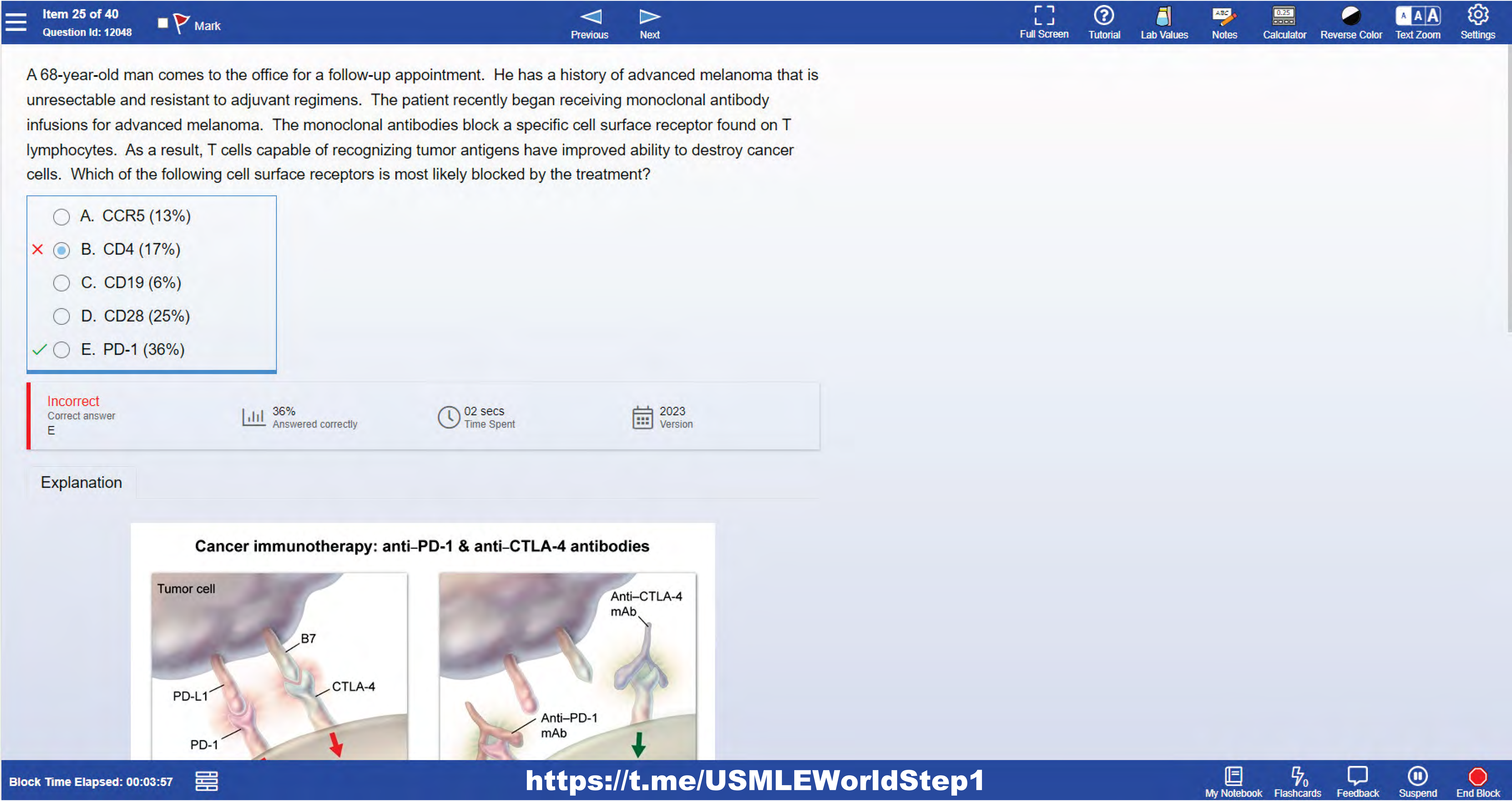
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○ A. CCR5 (13%)
✗ ● B. CD4 (17%)
○ C. CD19 (6%)
○ D. CD28 (25%)
✓ ○ E. PD-1 (36%)

Incorrect
Correct answer
E

36%
Answered correctly

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Explanation

Cancer immunotherapy: anti–PD-1 & anti–CTLA-4 antibodies

Tumor cell
B7
CTLA-4
PD-L1
PD-1
Anti–CTLA-4 mAb
Anti–PD-1 mAb

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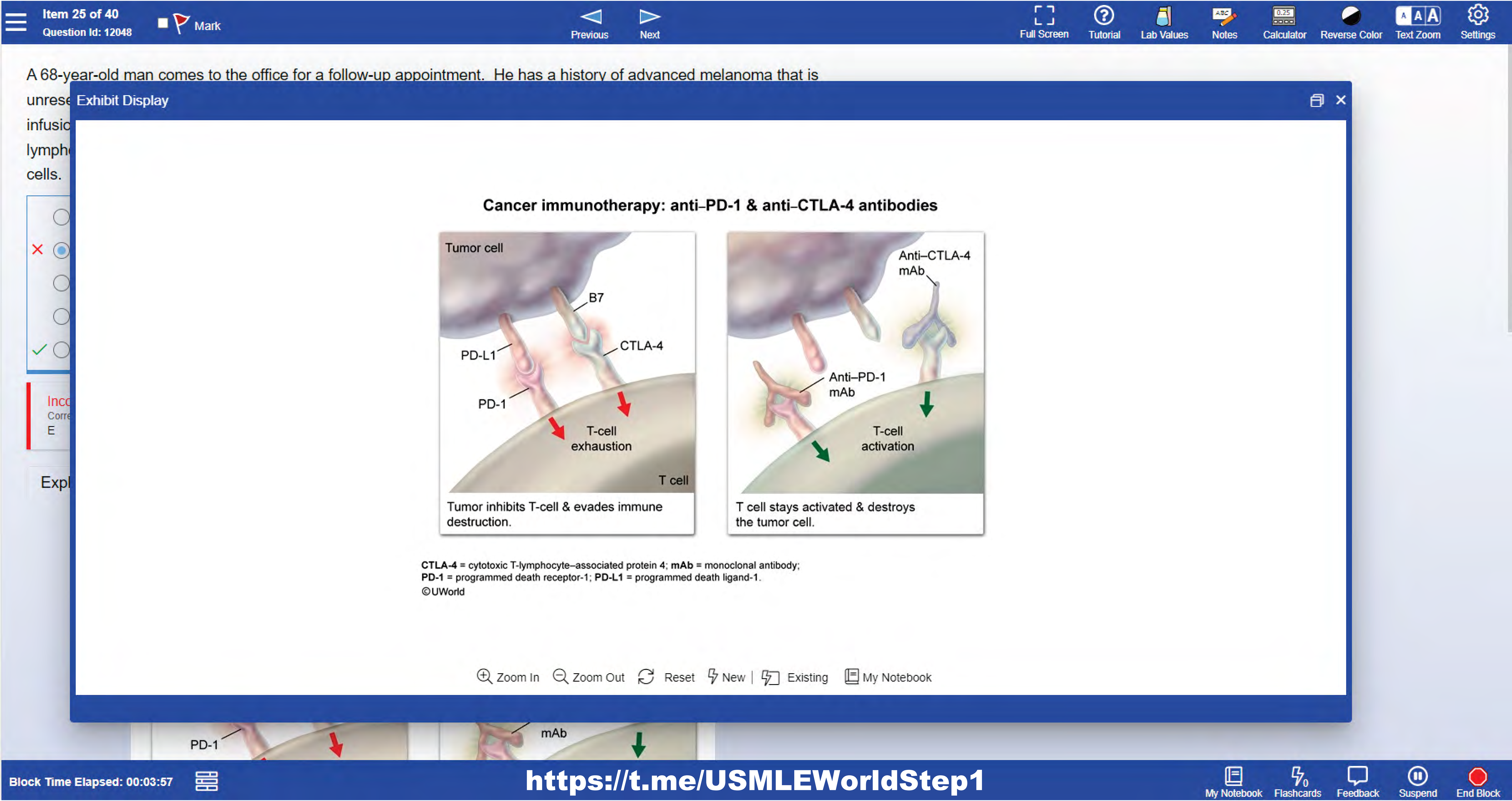
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A 68-year-old man comes to the office for a follow-up appointment. He has a history of advanced melanoma that is

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Cancer immunotherapy: anti–PD-1 & anti–CTLA-4 antibodies

Tumor cell
B7
CTLA-4
PD-L1
PD-1
T-cell exhaustion
T cell
Anti–CTLA-4 mAb
Anti–PD-1 mAb
T-cell activation

Tumor inhibits T-cell & evades immune destruction.

T cell stays activated & destroys the tumor cell.

CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; **mAb** = monoclonal antibody;
PD-1 = programmed death receptor-1; **PD-L1** = programmed death ligand-1.
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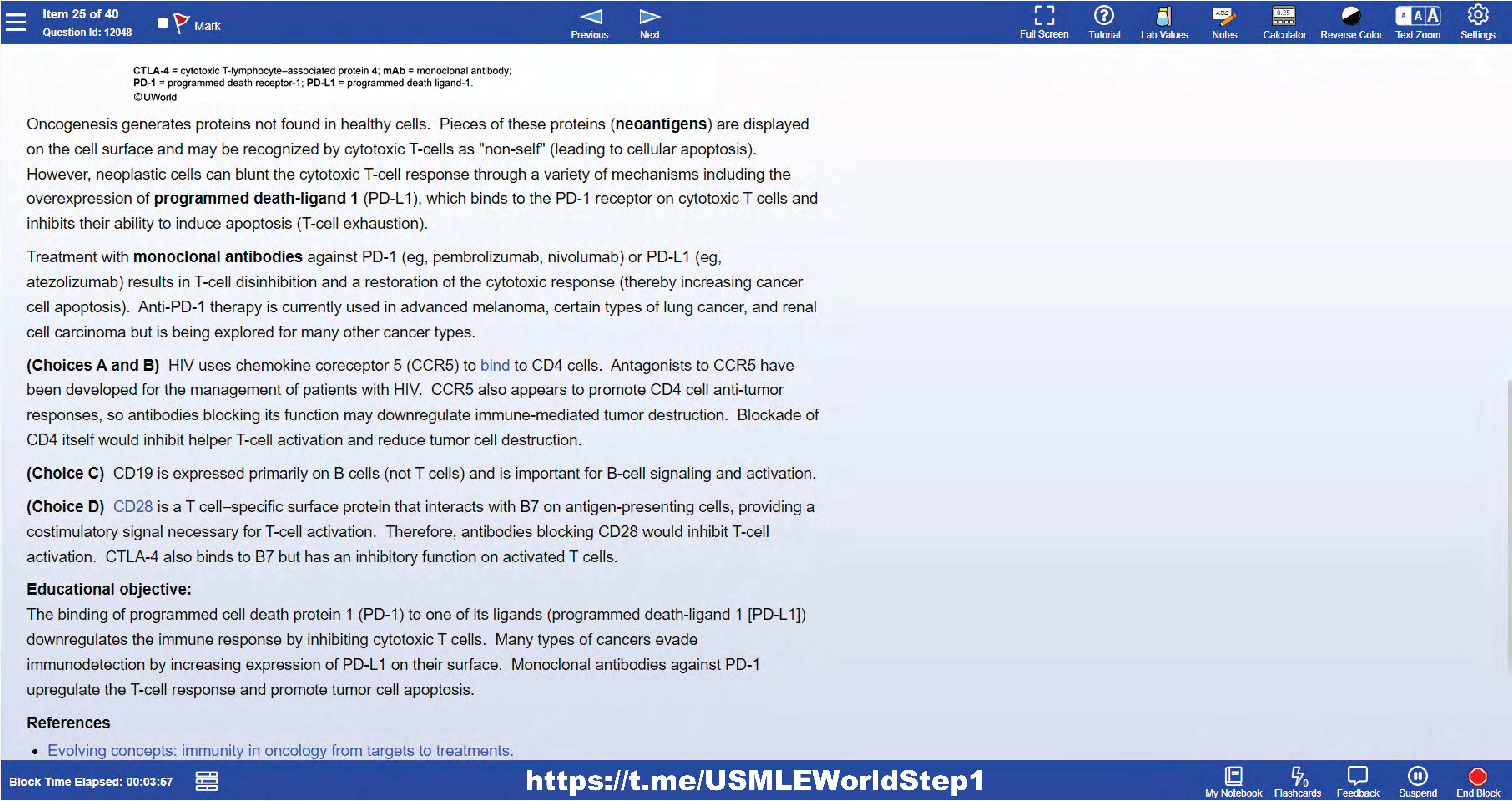

CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; **mAb** = monoclonal antibody;
PD-1 = programmed death receptor-1; **PD-L1** = programmed death ligand-1.
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Oncogenesis generates proteins not found in healthy cells. Pieces of these proteins (**neoantigens**) are displayed on the cell surface and may be recognized by cytotoxic T-cells as "non-self" (leading to cellular apoptosis). However, neoplastic cells can blunt the cytotoxic T-cell response through a variety of mechanisms including the overexpression of **programmed death-ligand 1** (PD-L1), which binds to the PD-1 receptor on cytotoxic T cells and inhibits their ability to induce apoptosis (T-cell exhaustion).

Treatment with **monoclonal antibodies** against PD-1 (eg, pembrolizumab, nivolumab) or PD-L1 (eg, atezolizumab) results in T-cell disinhibition and a restoration of the cytotoxic response (thereby increasing cancer cell apoptosis). Anti-PD-1 therapy is currently used in advanced melanoma, certain types of lung cancer, and renal cell carcinoma but is being explored for many other cancer types.

(Choices A and B) HIV uses chemokine coreceptor 5 (CCR5) to bind to CD4 cells. Antagonists to CCR5 have been developed for the management of patients with HIV. CCR5 also appears to promote CD4 cell anti-tumor responses, so antibodies blocking its function may downregulate immune-mediated tumor destruction. Blockade of CD4 itself would inhibit helper T-cell activation and reduce tumor cell destruction.

(Choice C) CD19 is expressed primarily on B cells (not T cells) and is important for B-cell signaling and activation.

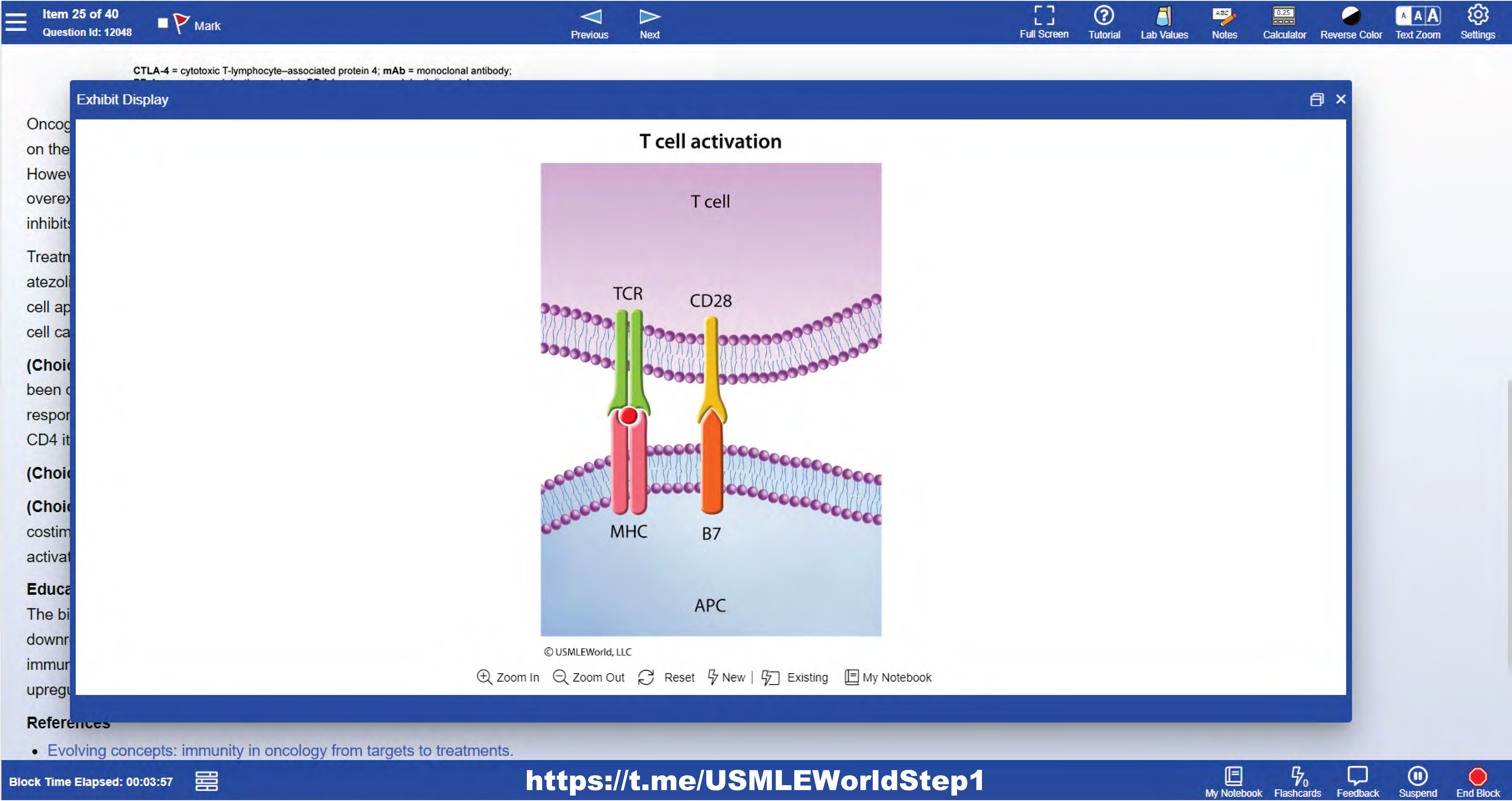
(Choice D) CD28 is a T cell–specific surface protein that interacts with B7 on antigen-presenting cells, providing a costimulatory signal necessary for T-cell activation. Therefore, antibodies blocking CD28 would inhibit T-cell activation. CTLA-4 also binds to B7 but has an inhibitory function on activated T cells.

Educational objective:

The binding of programmed cell death protein 1 (PD-1) to one of its ligands (programmed death-ligand 1 [PD-L1]) downregulates the immune response by inhibiting cytotoxic T cells. Many types of cancers evade immunodetection by increasing expression of PD-L1 on their surface. Monoclonal antibodies against PD-1 upregulate the T-cell response and promote tumor cell apoptosis.

References

- Evolving concepts: immunity in oncology from targets to treatments.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CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; **mAb** = monoclonal antibody;

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- Evolving concepts: immunity in oncology from targets to treatments.

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T cell activation

T cell
TCR
CD28
MHC
B7
APC

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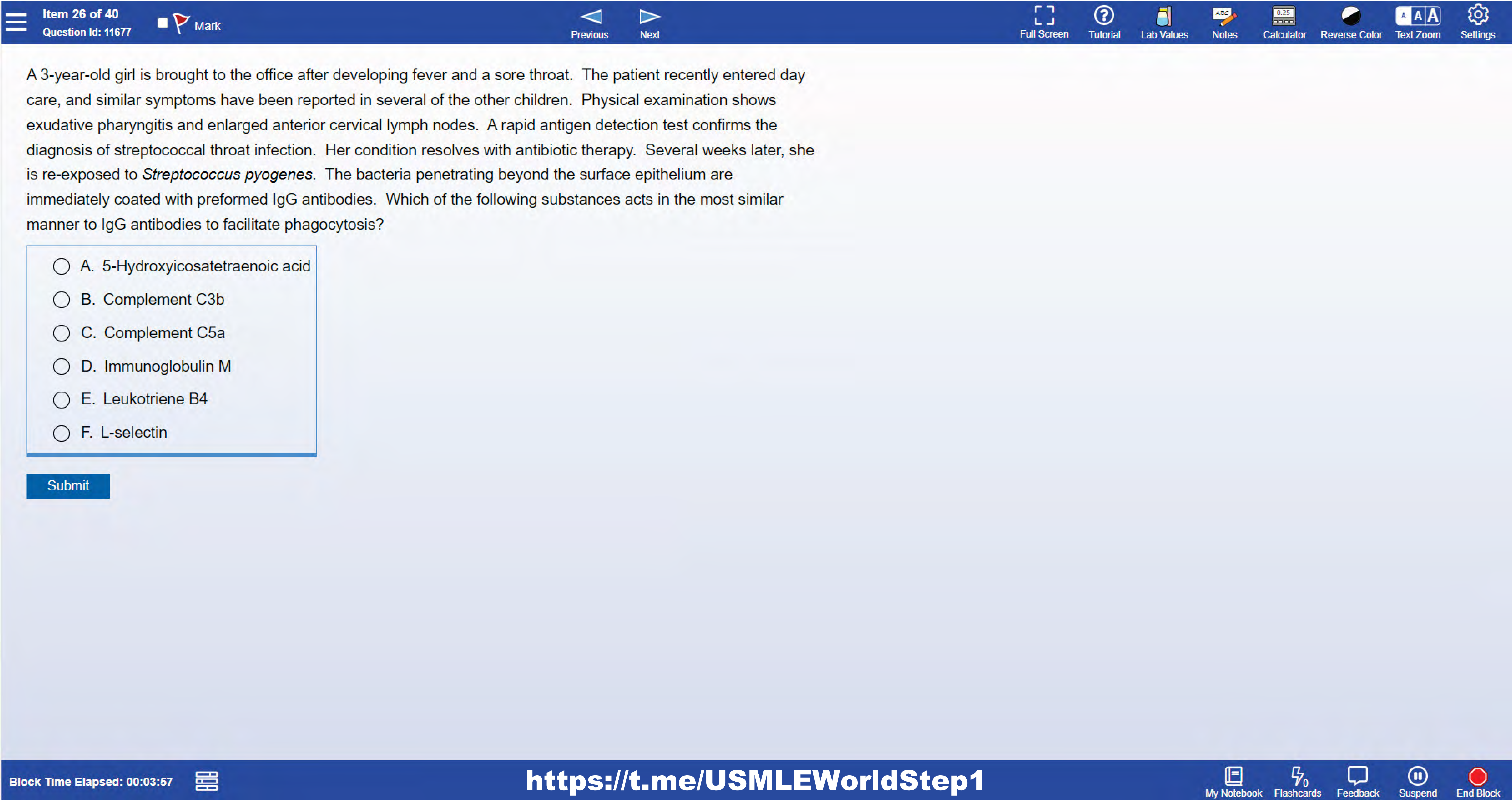
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A 3-year-old girl is brought to the office after developing fever and a sore throat. The patient recently entered day care, and similar symptoms have been reported in several of the other children. Physical examination shows exudative pharyngitis and enlarged anterior cervical lymph nodes. A rapid antigen detection test confirms the diagnosis of streptococcal throat infection. Her condition resolves with antibiotic therapy. Several weeks later, she is re-exposed to *Streptococcus pyogenes*. The bacteria penetrating beyond the surface epithelium are immediately coated with preformed IgG antibodies. Which of the following substances acts in the most similar manner to IgG antibodies to facilitate phagocytosis?

○ A. 5-Hydroxyicosatetraenoic acid
○ B. Complement C3b
○ C. Complement C5a
○ D. Immunoglobulin M
○ E. Leukotriene B4
○ F. L-selectin

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A 3-year-old girl is brought to the office after developing fever and a sore throat. The patient recently entered day care, and similar symptoms have been reported in several of the other children. Physical examination shows exudative pharyngitis and enlarged anterior cervical lymph nodes. A rapid antigen detection test confirms the diagnosis of streptococcal throat infection. Her condition resolves with antibiotic therapy. Several weeks later, she is re-exposed to *Streptococcus pyogenes*. The bacteria penetrating beyond the surface epithelium are immediately coated with preformed IgG antibodies. Which of the following substances acts in the most similar manner to IgG antibodies to facilitate phagocytosis?

○ A. 5-Hydroxyicosatetraenoic acid (0%)
✓ ● B. Complement C3b (78%)
○ C. Complement C5a (8%)
○ D. Immunoglobulin M (9%)
○ E. Leukotriene B4 (1%)
○ F. L-selectin (1%)

Correct

78% Answered correctly

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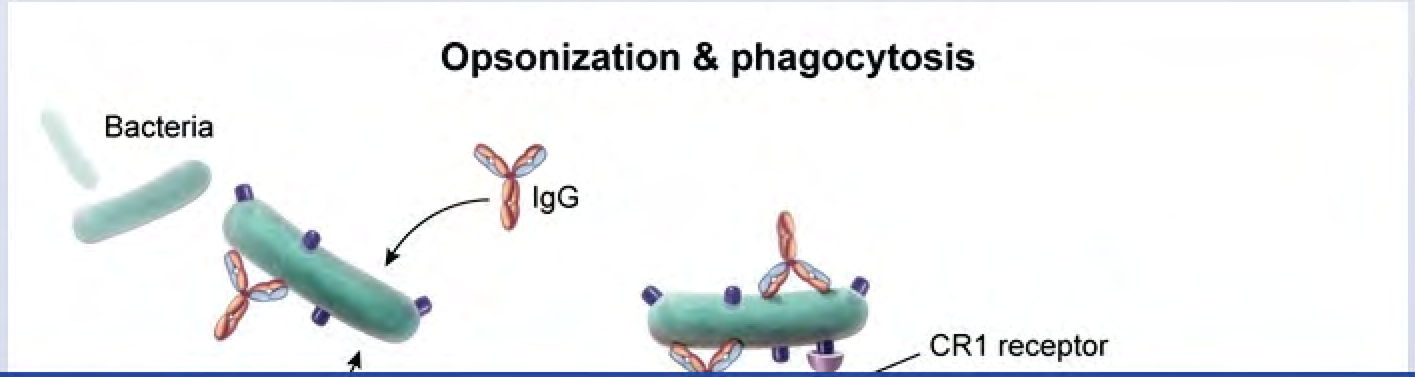
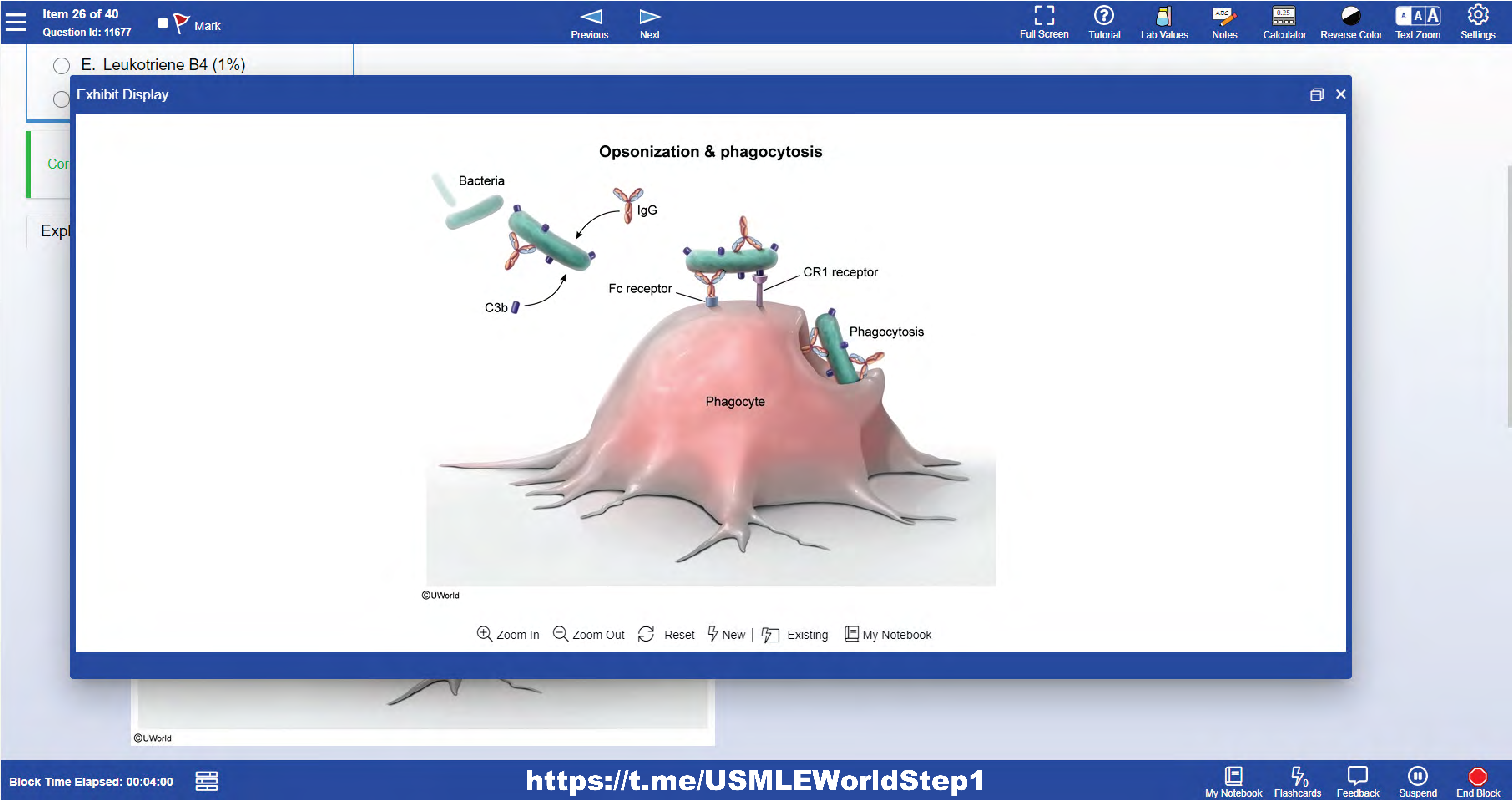
Explanation





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○ E. Leukotriene B4 (1%)

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Opsonization & phagocytosis

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Settings
Bacteria
IgG
C3b
Fc receptor
CR1 receptor
Phagocytosis
Phagocyte
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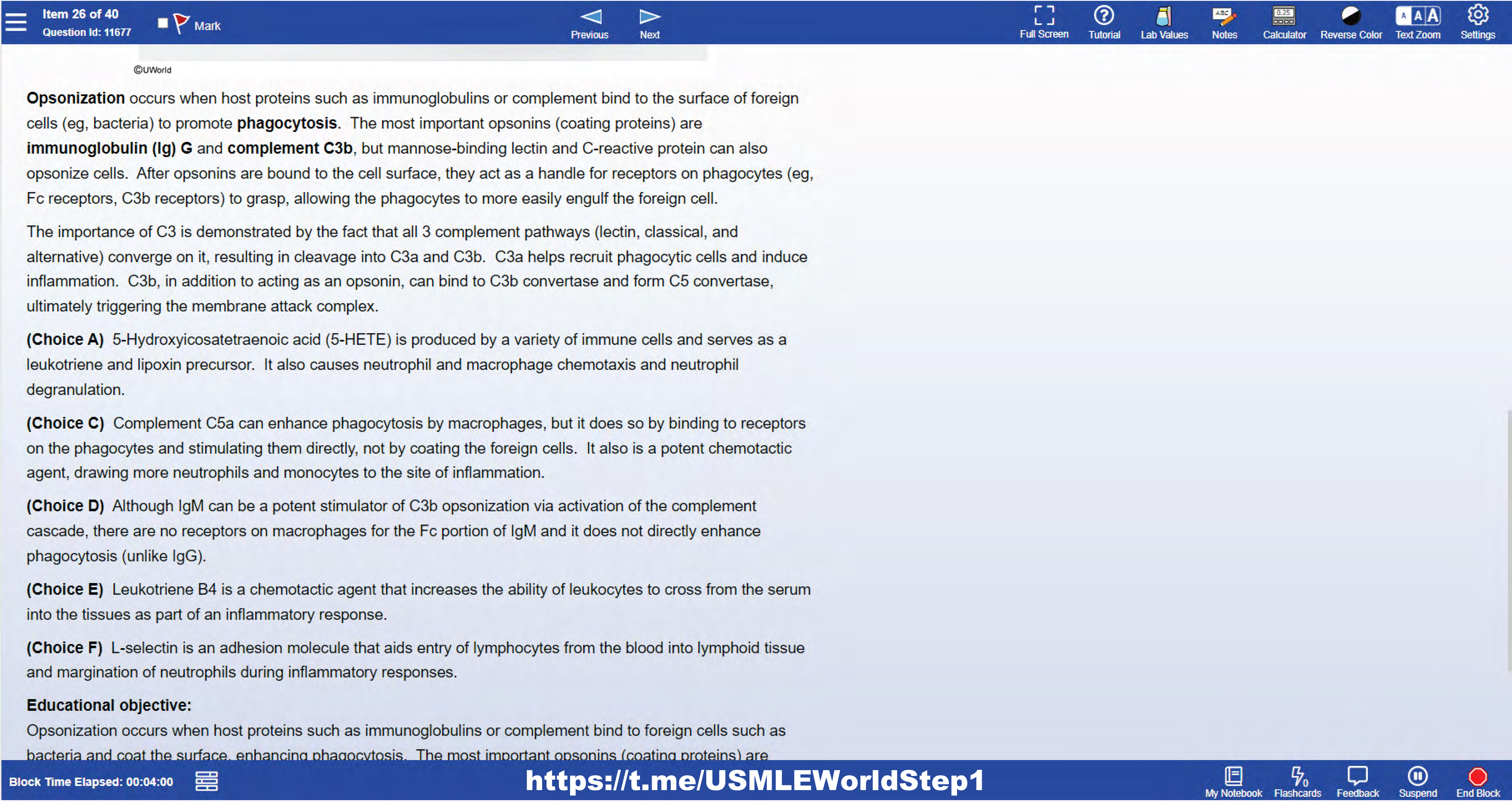

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Opsonization occurs when host proteins such as immunoglobulins or complement bind to the surface of foreign cells (eg, bacteria) to promote **phagocytosis**. The most important opsonins (coating proteins) are **immunoglobulin (Ig) G** and **complement C3b**, but mannose-binding lectin and C-reactive protein can also opsonize cells. After opsonins are bound to the cell surface, they act as a handle for receptors on phagocytes (eg, Fc receptors, C3b receptors) to grasp, allowing the phagocytes to more easily engulf the foreign cell.

The importance of C3 is demonstrated by the fact that all 3 complement pathways (lectin, classical, and alternative) converge on it, resulting in cleavage into C3a and C3b. C3a helps recruit phagocytic cells and induce inflammation. C3b, in addition to acting as an opsonin, can bind to C3b convertase and form C5 convertase, ultimately triggering the membrane attack complex.

(Choice A) 5-Hydroxyicosatetraenoic acid (5-HETE) is produced by a variety of immune cells and serves as a leukotriene and lipoxin precursor. It also causes neutrophil and macrophage chemotaxis and neutrophil degranulation.

(Choice C) Complement C5a can enhance phagocytosis by macrophages, but it does so by binding to receptors on the phagocytes and stimulating them directly, not by coating the foreign cells. It also is a potent chemotactic agent, drawing more neutrophils and monocytes to the site of inflammation.

(Choice D) Although IgM can be a potent stimulator of C3b opsonization via activation of the complement cascade, there are no receptors on macrophages for the Fc portion of IgM and it does not directly enhance phagocytosis (unlike IgG).

(Choice E) Leukotriene B4 is a chemotactic agent that increases the ability of leukocytes to cross from the serum into the tissues as part of an inflammatory response.

(Choice F) L-selectin is an adhesion molecule that aids entry of lymphocytes from the blood into lymphoid tissue and margination of neutrophils during inflammatory responses.

Educational objective:

Opsonization occurs when host proteins such as immunoglobulins or complement bind to foreign cells such as bacteria and coat the surface, enhancing phagocytosis. The most important opsonins (coating proteins) are

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Educational objective:
Opsonization occurs when host proteins such as immunoglobulins or complement bind to foreign cells such as bacteria and coat the surface, enhancing phagocytosis. The most important opsonins (coating proteins) are immunoglobulin G and complement C3b.

References

- Neutrophils and macrophages work in concert as inducers and effectors of adaptive immunity against

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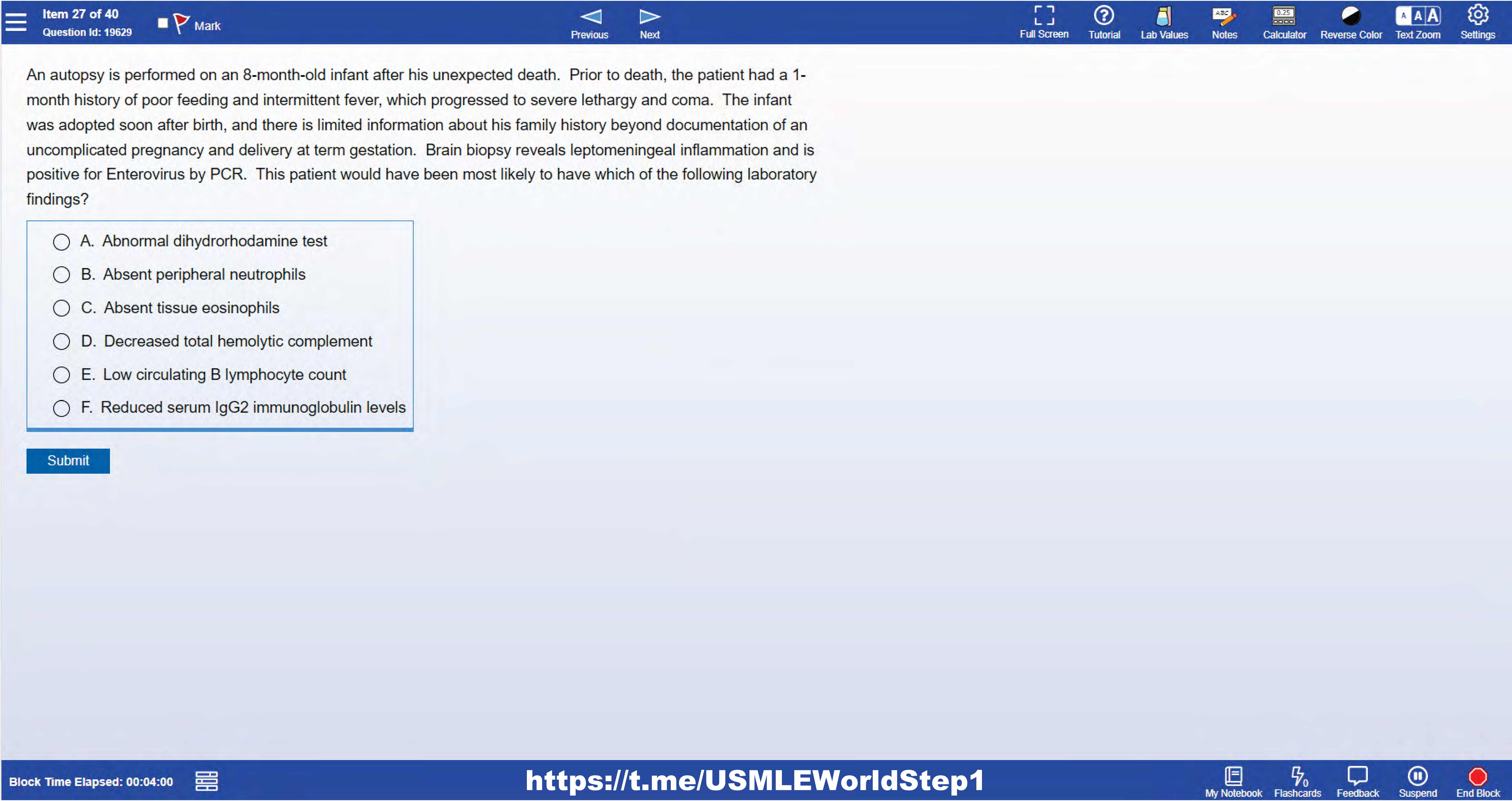
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An autopsy is performed on an 8-month-old infant after his unexpected death. Prior to death, the patient had a 1-month history of poor feeding and intermittent fever, which progressed to severe lethargy and coma. The infant was adopted soon after birth, and there is limited information about his family history beyond documentation of an uncomplicated pregnancy and delivery at term gestation. Brain biopsy reveals leptomeningeal inflammation and is positive for Enterovirus by PCR. This patient would have been most likely to have which of the following laboratory findings?

○ A. Abnormal dihydrorhodamine test
○ B. Absent peripheral neutrophils
○ C. Absent tissue eosinophils
○ D. Decreased total hemolytic complement
○ E. Low circulating B lymphocyte count
○ F. Reduced serum IgG2 immunoglobulin levels

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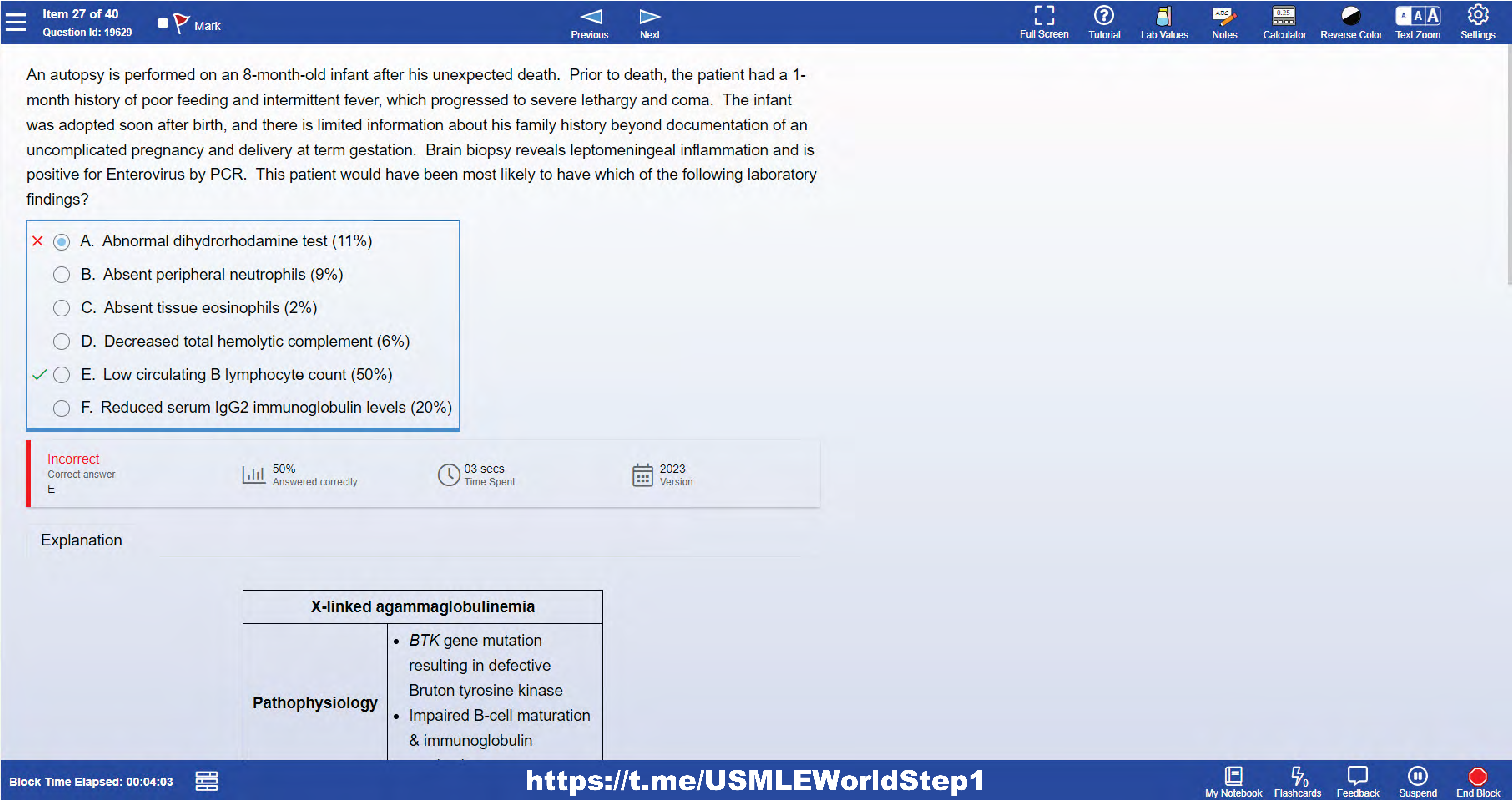
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- ✗ ● A. Abnormal dihydrorhodamine test (11%)
- ○ B. Absent peripheral neutrophils (9%)
- ○ C. Absent tissue eosinophils (2%)
- ○ D. Decreased total hemolytic complement (6%)
- ✓ ○ E. Low circulating B lymphocyte count (50%)
- ○ F. Reduced serum IgG2 immunoglobulin levels (20%)

Incorrect
Correct answer
E

50%
Answered correctly

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Explanation

X-linked agammaglobulinemia	
Pathophysiology	- *BTK* gene mutation resulting in defective Bruton tyrosine kinase - Impaired B-cell maturation & immunoglobulin

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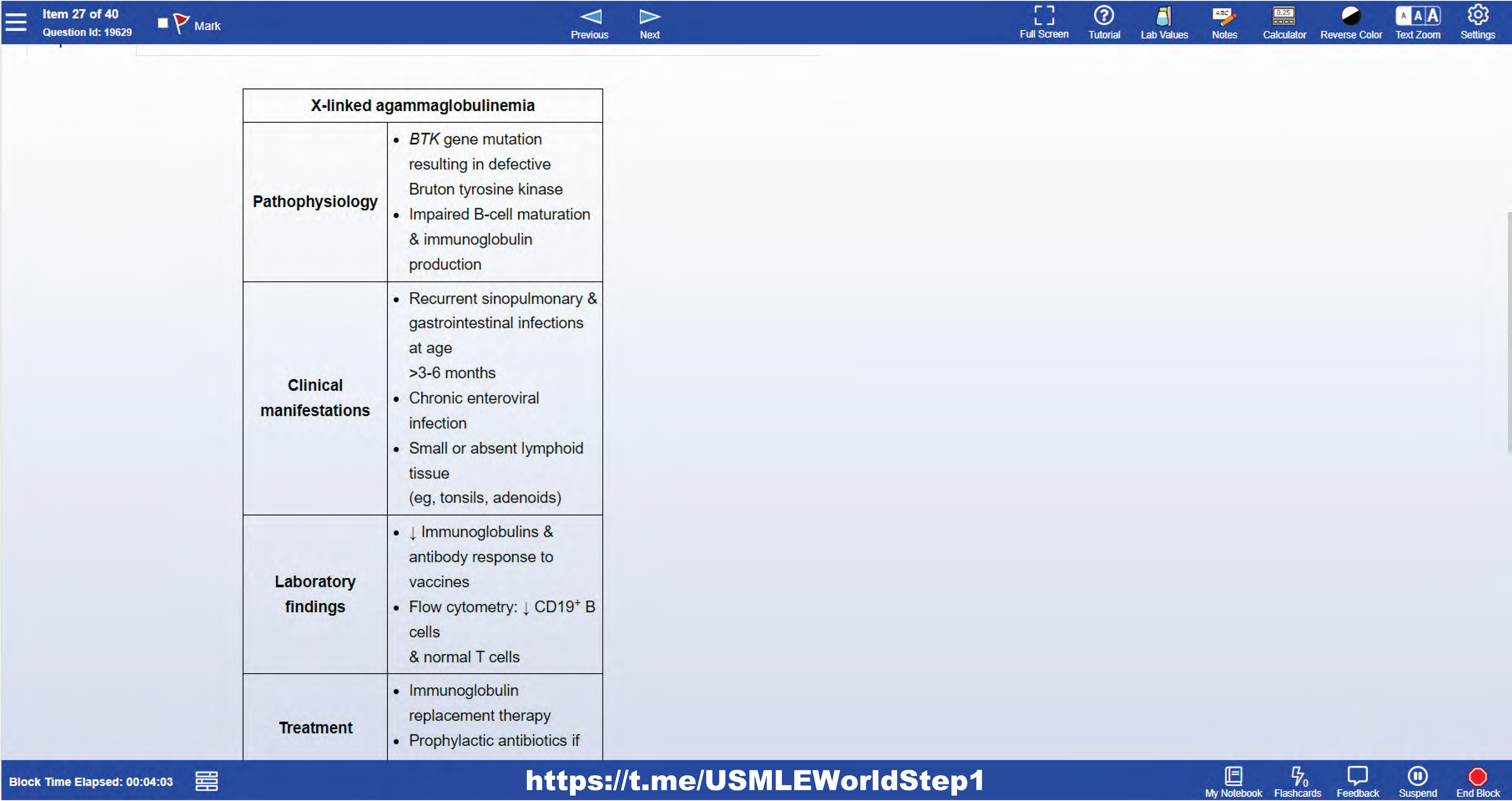
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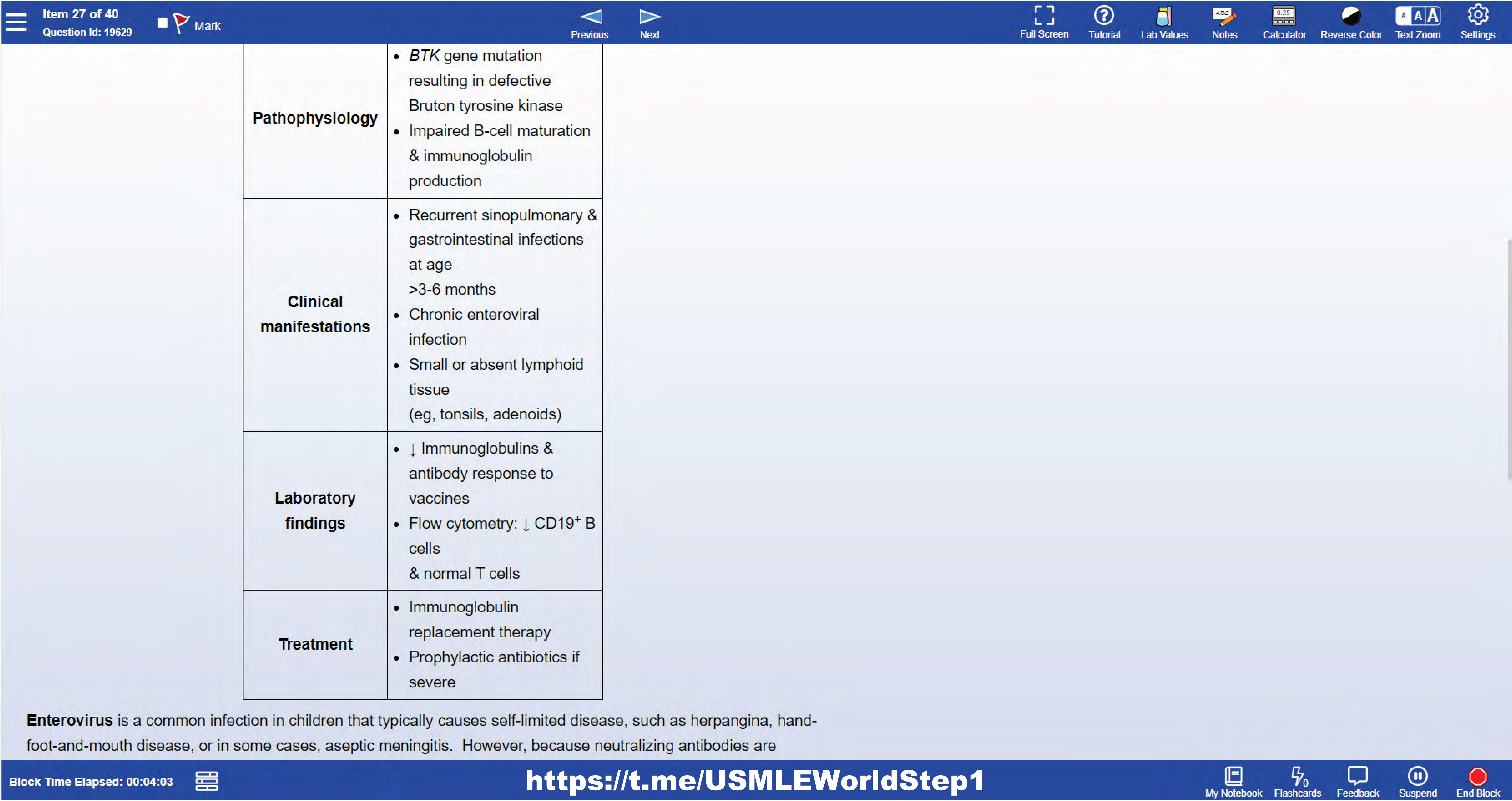
X-linked agammaglobulinemia	
Pathophysiology	- *BTK* gene mutation resulting in defective Bruton tyrosine kinase - Impaired B-cell maturation & immunoglobulin production
Clinical manifestations	- Recurrent sinopulmonary & gastrointestinal infections at age >3-6 months - Chronic enteroviral infection - Small or absent lymphoid tissue (eg, tonsils, adenoids)
Laboratory findings	- ↓ Immunoglobulins & antibody response to vaccines - Flow cytometry: ↓ $CD19^+$ B cells & normal T cells
Treatment	- Immunoglobulin replacement therapy - Prophylactic antibiotics if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Pathophysiology	• *BTK* gene mutation resulting in defective Bruton tyrosine kinase • Impaired B-cell maturation & immunoglobulin production
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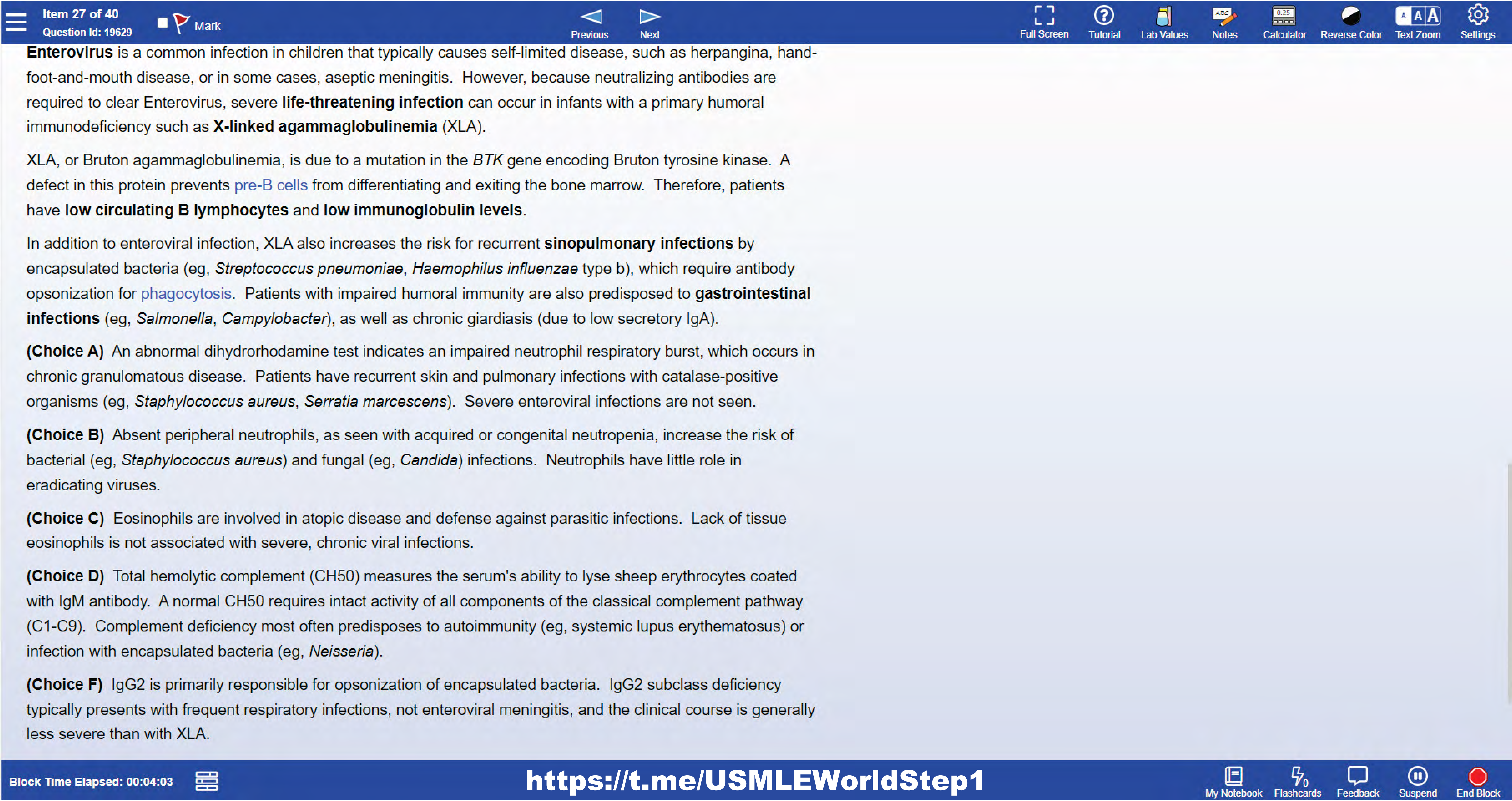
Laboratory findings	• ↓ Immunoglobulins & antibody response to vaccines • Flow cytometry: ↓ CD19$^+$ B cells & normal T cells
Treatment	• Immunoglobulin replacement therapy • Prophylactic antibiotics if severe

Enterovirus is a common infection in children that typically causes self-limited disease, such as herpangina, hand-foot-and-mouth disease, or in some cases, aseptic meningitis. However, because neutralizing antibodies are



Enterovirus is a common infection in children that typically causes self-limited disease, such as herpangina, hand-foot-and-mouth disease, or in some cases, aseptic meningitis. However, because neutralizing antibodies are required to clear Enterovirus, severe **life-threatening infection** can occur in infants with a primary humoral immunodeficiency such as **X-linked agammaglobulinemia** (XLA).

XLA, or Bruton agammaglobulinemia, is due to a mutation in the *BTK* gene encoding Bruton tyrosine kinase. A defect in this protein prevents pre-B cells from differentiating and exiting the bone marrow. Therefore, patients have **low circulating B lymphocytes** and **low immunoglobulin levels**.

In addition to enteroviral infection, XLA also increases the risk for recurrent **sinopulmonary infections** by encapsulated bacteria (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b), which require antibody opsonization for phagocytosis. Patients with impaired humoral immunity are also predisposed to **gastrointestinal infections** (eg, *Salmonella*, *Campylobacter*), as well as chronic giardiasis (due to low secretory IgA).

(Choice A) An abnormal dihydrorhodamine test indicates an impaired neutrophil respiratory burst, which occurs in chronic granulomatous disease. Patients have recurrent skin and pulmonary infections with catalase-positive organisms (eg, *Staphylococcus aureus*, *Serratia marcescens*). Severe enteroviral infections are not seen.

(Choice B) Absent peripheral neutrophils, as seen with acquired or congenital neutropenia, increase the risk of bacterial (eg, *Staphylococcus aureus*) and fungal (eg, *Candida*) infections. Neutrophils have little role in eradicating viruses.

(Choice C) Eosinophils are involved in atopic disease and defense against parasitic infections. Lack of tissue eosinophils is not associated with severe, chronic viral infections.

(Choice D) Total hemolytic complement (CH50) measures the serum's ability to lyse sheep erythrocytes coated with IgM antibody. A normal CH50 requires intact activity of all components of the classical complement pathway (C1-C9). Complement deficiency most often predisposes to autoimmunity (eg, systemic lupus erythematosus) or infection with encapsulated bacteria (eg, *Neisseria*).

(Choice F) IgG2 is primarily responsible for opsonization of encapsulated bacteria. IgG2 subclass deficiency typically presents with frequent respiratory infections, not enteroviral meningitis, and the clinical course is generally less severe than with XLA.

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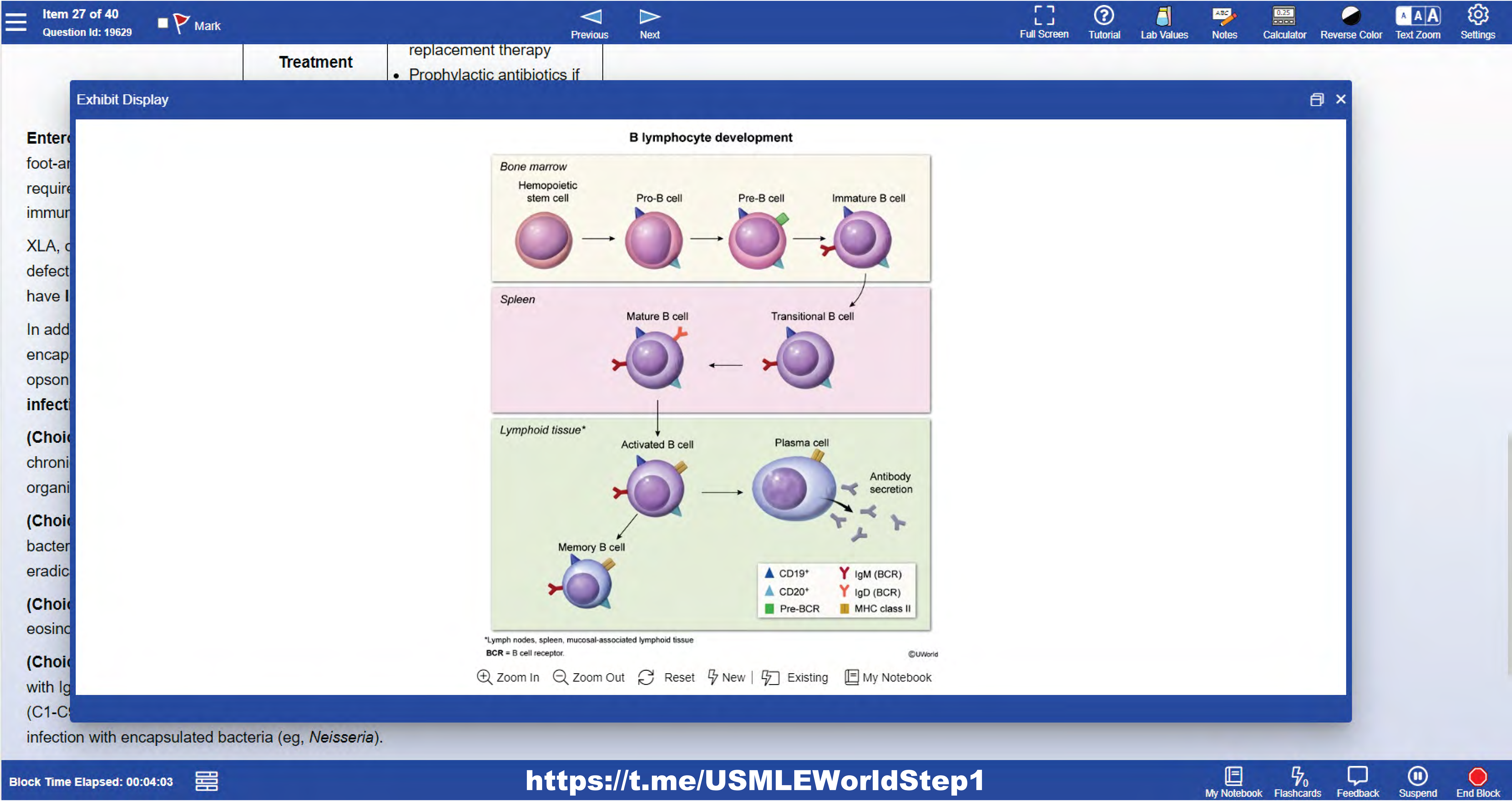
(Choice F) IgG2 is primarily responsible for opsonization of encapsulated bacteria. IgG2 subclass deficiency typically presents with frequent respiratory infections, not enteroviral meningitis, and the clinical course is generally less severe than with XLA.

Educational objective:
X-linked agammaglobulinemia, an immunodeficiency characterized by low circulating B lymphocytes and immunoglobulins, should be suspected in an infant with severe, life-threatening enteroviral infection.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Bone marrow
Hemopoietic stem cell
Pro-B cell
Pre-B cell
Immature B cell
Spleen
Mature B cell
Transitional B cell
Lymphoid tissue*
Activated B cell
Plasma cell
Antibody secretion
Memory B cell
CD19⁺
CD20⁺
Pre-BCR
IgM (BCR)
IgD (BCR)
MHC class II
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infection with encapsulated bacteria (eg, *Neisseria*).

B lymphocyte development

*Lymph nodes, spleen, mucosal-associated lymphoid tissue

BCR = B cell receptor.

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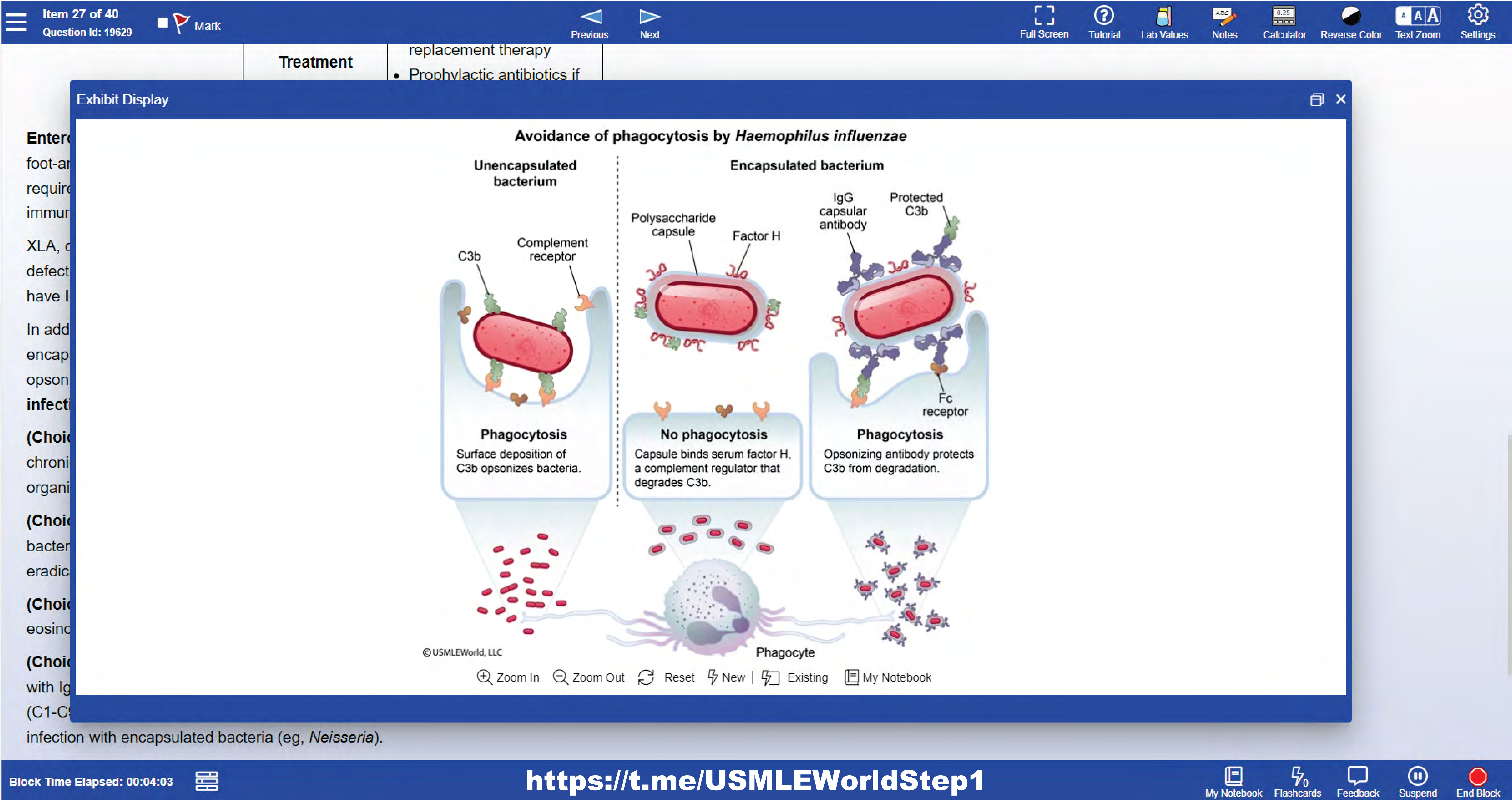

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Treatment	replacement therapy • Prophylactic antibiotics if

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infection with encapsulated bacteria (eg, *Neisseria*).

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Avoidance of phagocytosis by *Haemophilus influenzae*

Unencapsulated bacterium
Encapsulated bacterium
C3b
Complement receptor
Polysaccharide capsule
Factor H
IgG capsular antibody
Protected C3b
Fc receptor
Phagocyte

Phagocytosis
Surface deposition of C3b opsonizes bacteria.

No phagocytosis
Capsule binds serum factor H, a complement regulator that degrades C3b.

Phagocytosis
Opsonizing antibody protects C3b from degradation.

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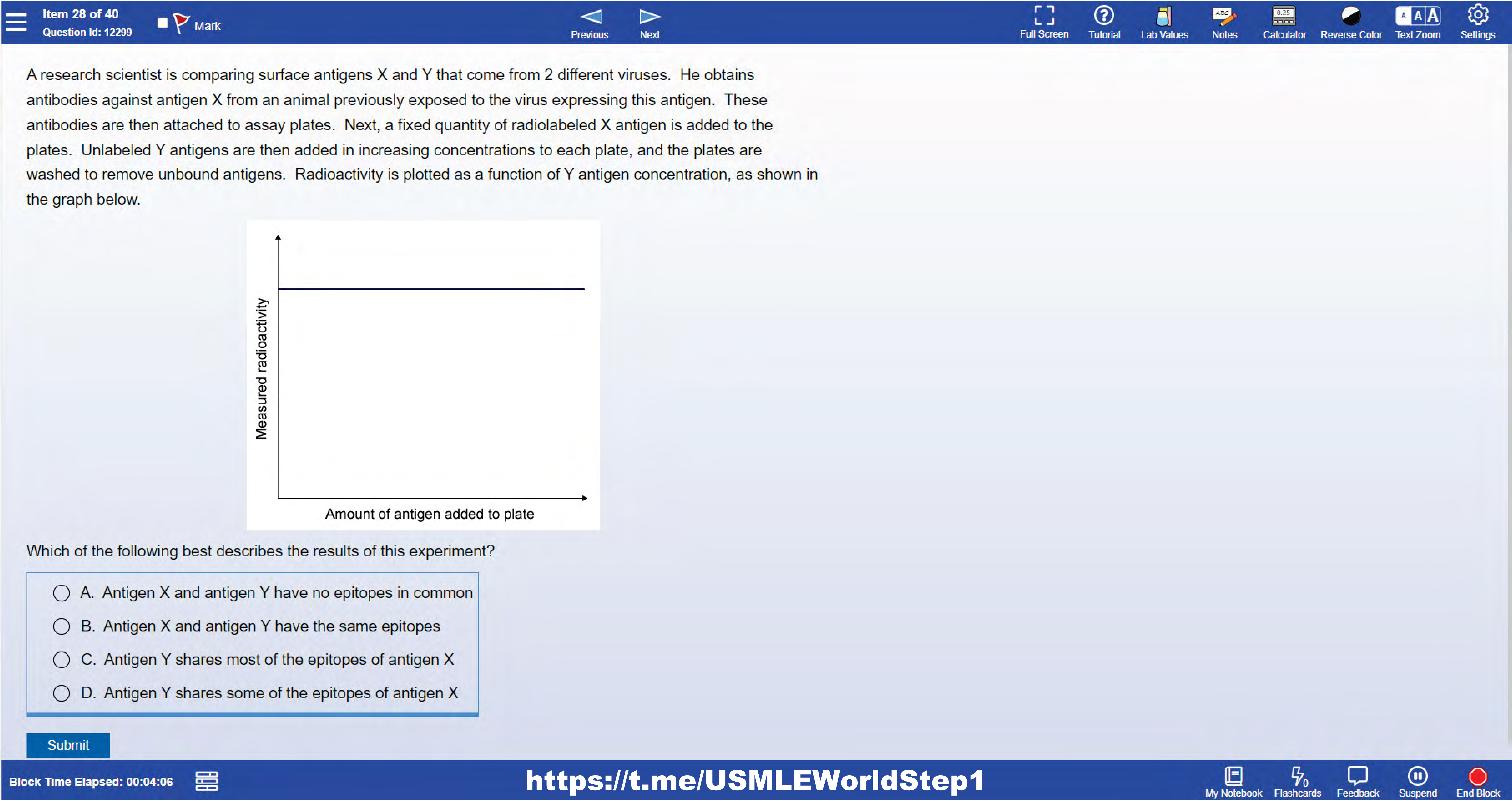
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Measured radioactivity
Amount of antigen added to plate
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A research scientist is comparing surface antigens X and Y that come from 2 different viruses. He obtains antibodies against antigen X from an animal previously exposed to the virus expressing this antigen. These antibodies are then attached to assay plates. Next, a fixed quantity of radiolabeled X antigen is added to the plates. Unlabeled Y antigens are then added in increasing concentrations to each plate, and the plates are washed to remove unbound antigens. Radioactivity is plotted as a function of Y antigen concentration, as shown in the graph below.

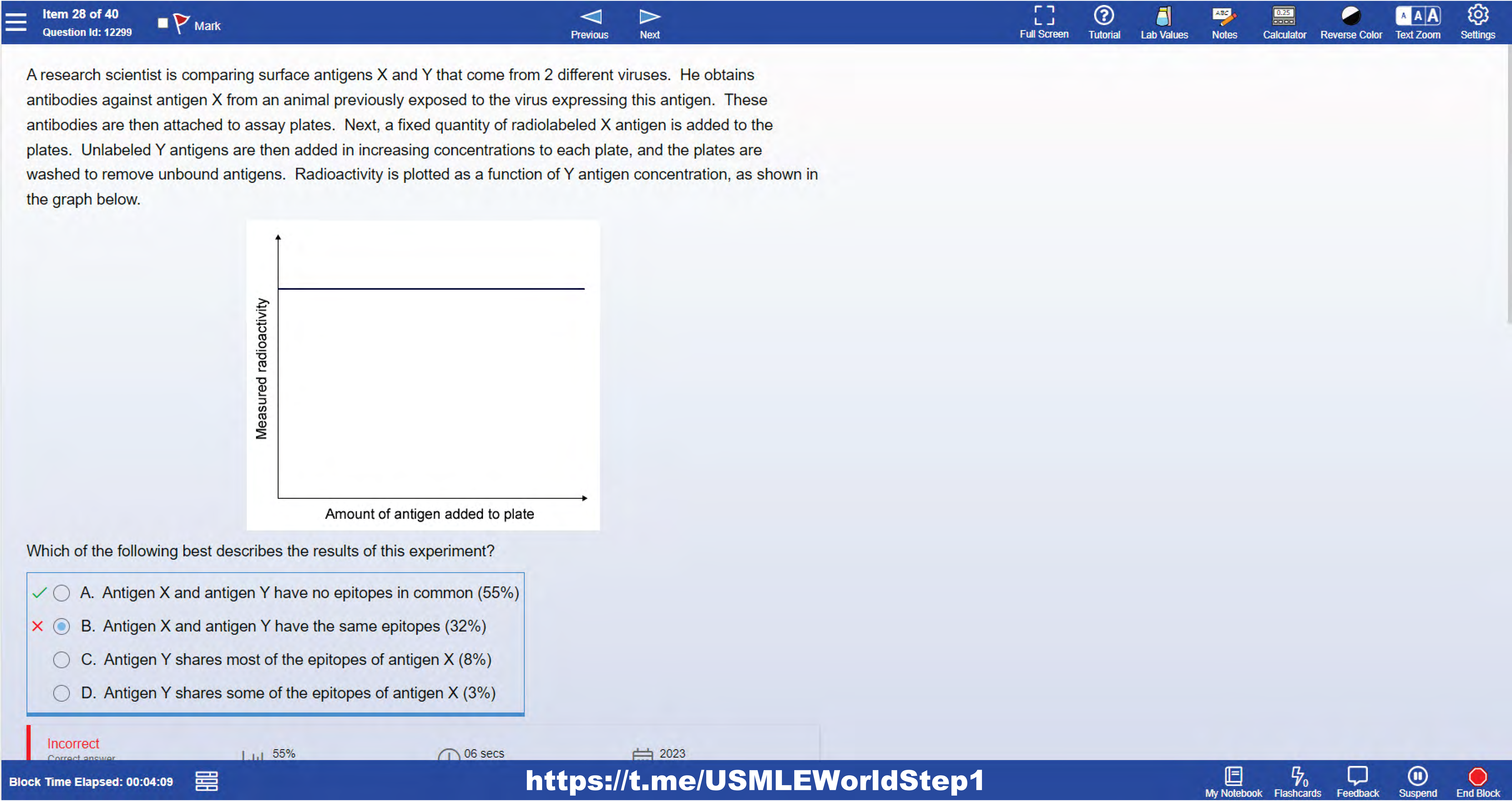
Which of the following best describes the results of this experiment?

○ A. Antigen X and antigen Y have no epitopes in common

○ B. Antigen X and antigen Y have the same epitopes

○ C. Antigen Y shares most of the epitopes of antigen X

○ D. Antigen Y shares some of the epitopes of antigen X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Amount of antigen added to plate
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Which of the following best describes the results of this experiment?

- ✓ ○ A. Antigen X and antigen Y have no epitopes in common (55%)
- ✗ ● B. Antigen X and antigen Y have the same epitopes (32%)
- ○ C. Antigen Y shares most of the epitopes of antigen X (8%)
- ○ D. Antigen Y shares some of the epitopes of antigen X (3%)

Incorrect
Correct answer

55%

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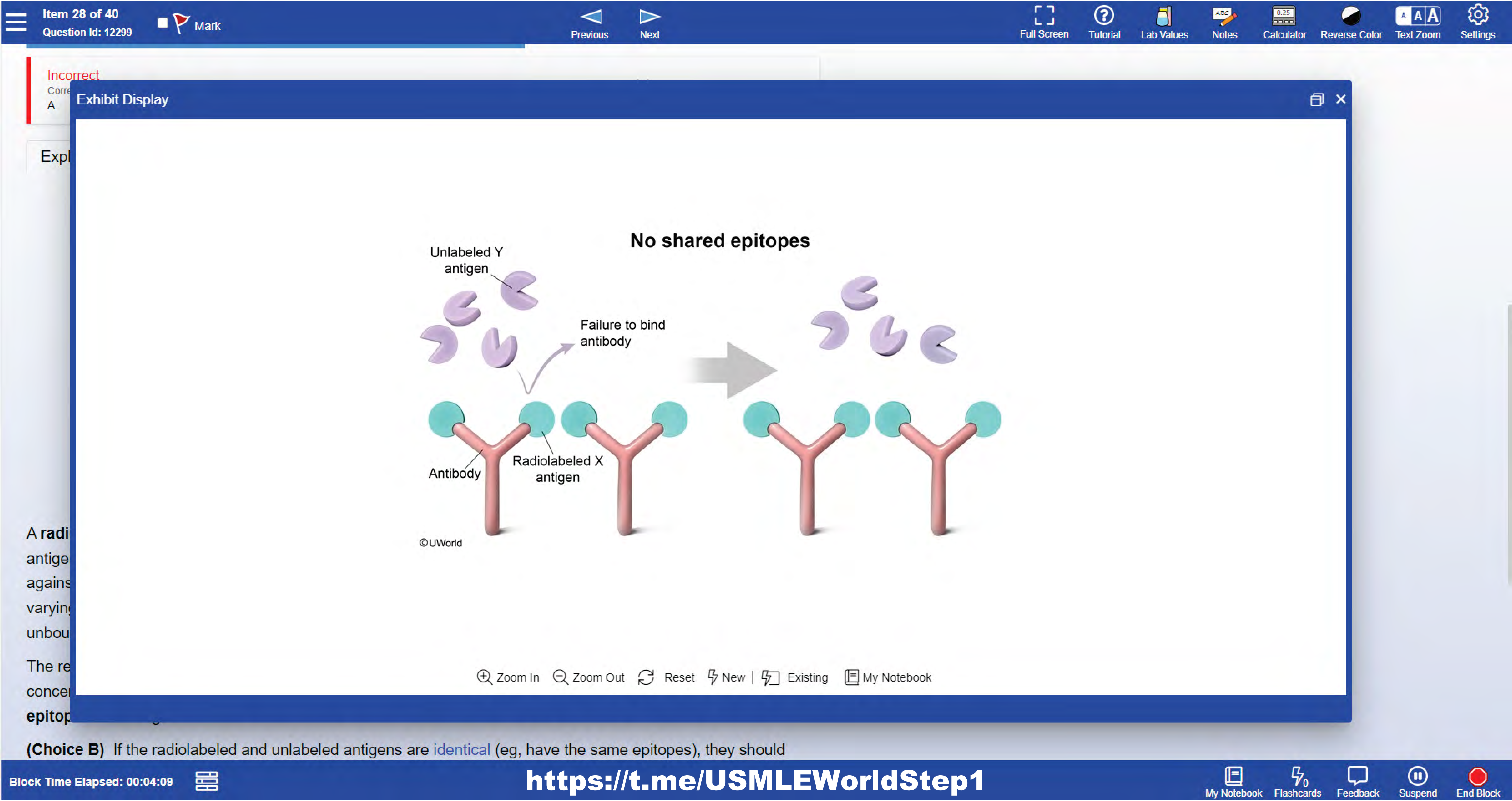
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No shared epitopes
Unlabeled Y antigen
Failure to bind antibody
Antibody
Radiolabeled X antigen
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(Choice B) If the radiolabeled and unlabeled antigens are identical (eg, have the same epitopes), they should

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A **radioimmunoassay** is a laboratory technique that uses specific antibodies and a known quantity of radiolabeled antigen to determine the amount of antigen present in an unknown sample. In this technique, specific **antibodies** against a known antigen are attached to an assay plate. Next, a fixed quantity of **radiolabeled antigen** and varying quantities of **unlabeled antigen** are added to the plate. The system is subsequently washed to remove unbound antigens, and radioactivity is measured.

The researcher in the above experiment observes no change in radioactivity with increasing Y antigen concentrations. This indicates that antigen Y cannot bind the available antibodies and therefore **shares no epitopes** with antigen X.

(Choice B) If the radiolabeled and unlabeled antigens are identical (eg, have the same epitopes), they should compete equally for antibody binding sites. The amount of radiolabeled antigen displaced from the antibodies will be proportionate to the amount of unlabeled antigen added. Consequently, increasing concentrations of antigen Y would result in a proportionate decrease in measured radioactivity.

(Choices C and D) If antigen Y shared most or some of the epitopes of antigen X, then antigen Y would bind at a rate proportionate to both the amount of antibodies able to recognize the common epitopes and the amount of antigen Y added to the system.

Educational objective:
A radioimmunoassay uses specific antibodies and a fixed quantity of radiolabeled antigen to determine the amount of antigen present in an unknown sample. This is done by measuring the amount of radiolabeled antigen displaced from the antibodies in the system.

References

- Radioimmunoassay.
- Radioimmunoassay: review of basic principles.

Immunology	Allergy & Immunology	Immunology principles
Subject	System	Topic

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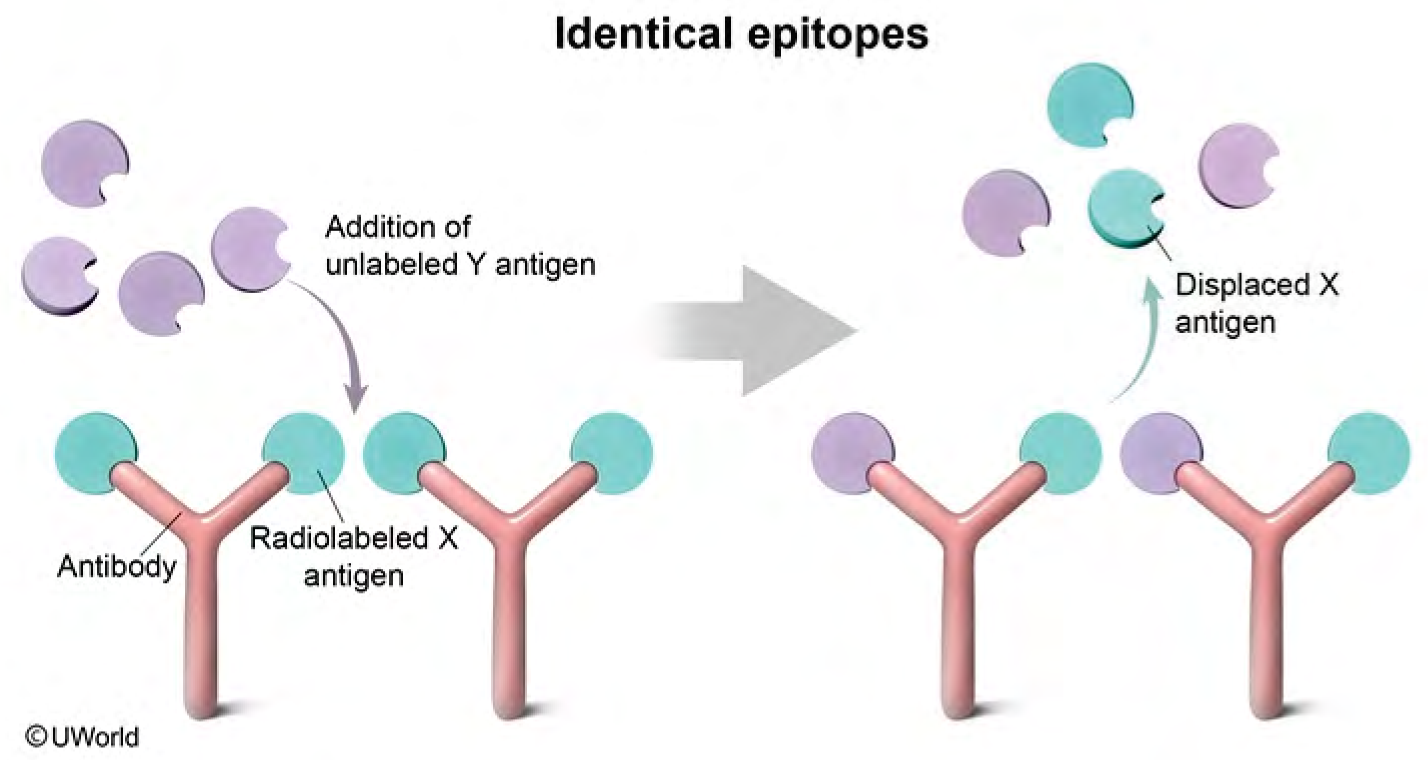
Identical epitopes
Addition of unlabeled Y antigen
Antibody
Radiolabeled X antigen
Displaced X antigen
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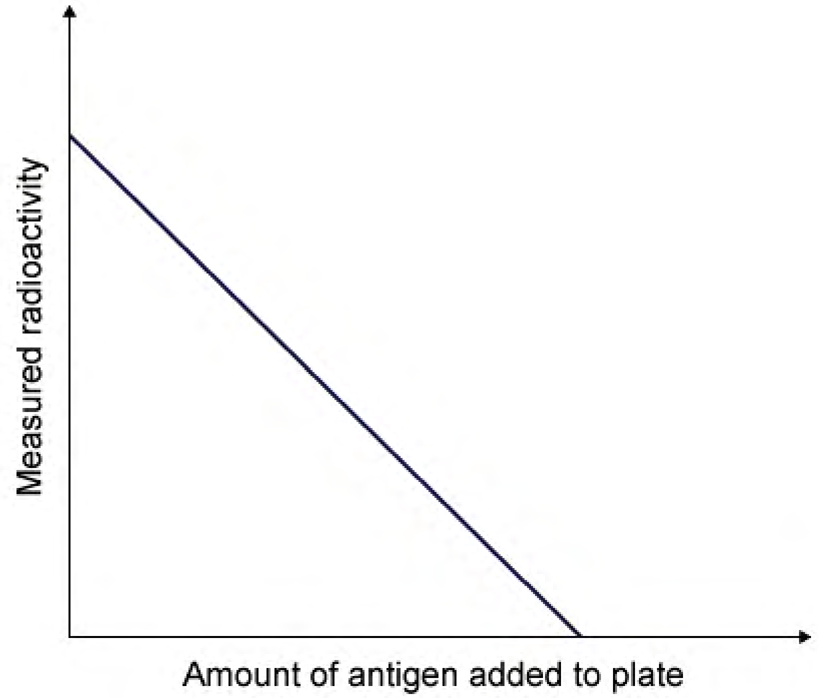

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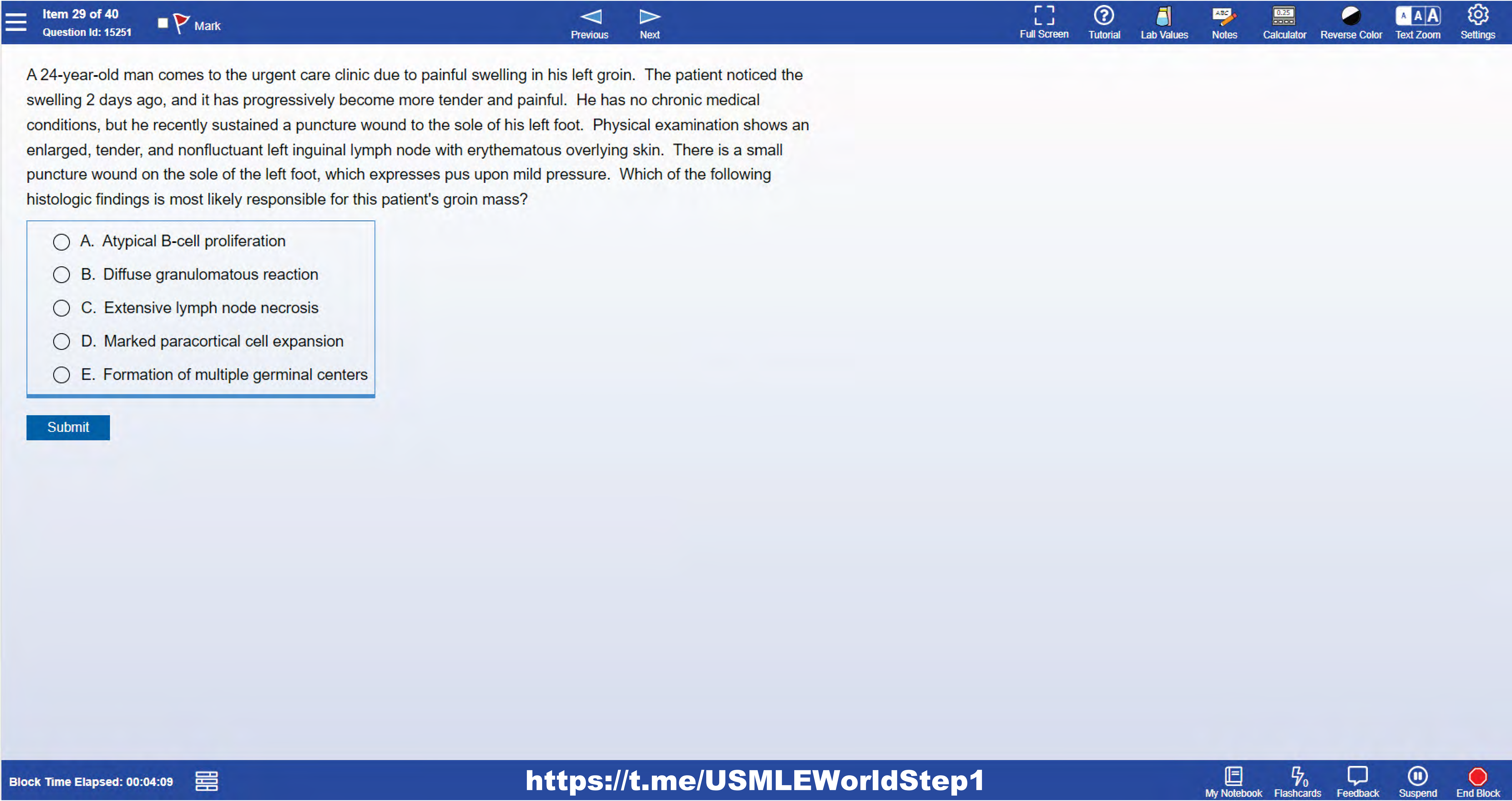
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A 24-year-old man comes to the urgent care clinic due to painful swelling in his left groin. The patient noticed the swelling 2 days ago, and it has progressively become more tender and painful. He has no chronic medical conditions, but he recently sustained a puncture wound to the sole of his left foot. Physical examination shows an enlarged, tender, and nonfluctuant left inguinal lymph node with erythematous overlying skin. There is a small puncture wound on the sole of the left foot, which expresses pus upon mild pressure. Which of the following histologic findings is most likely responsible for this patient's groin mass?

- ○ A. Atypical B-cell proliferation
- ○ B. Diffuse granulomatous reaction
- ○ C. Extensive lymph node necrosis
- ○ D. Marked paracortical cell expansion
- ○ E. Formation of multiple germinal centers

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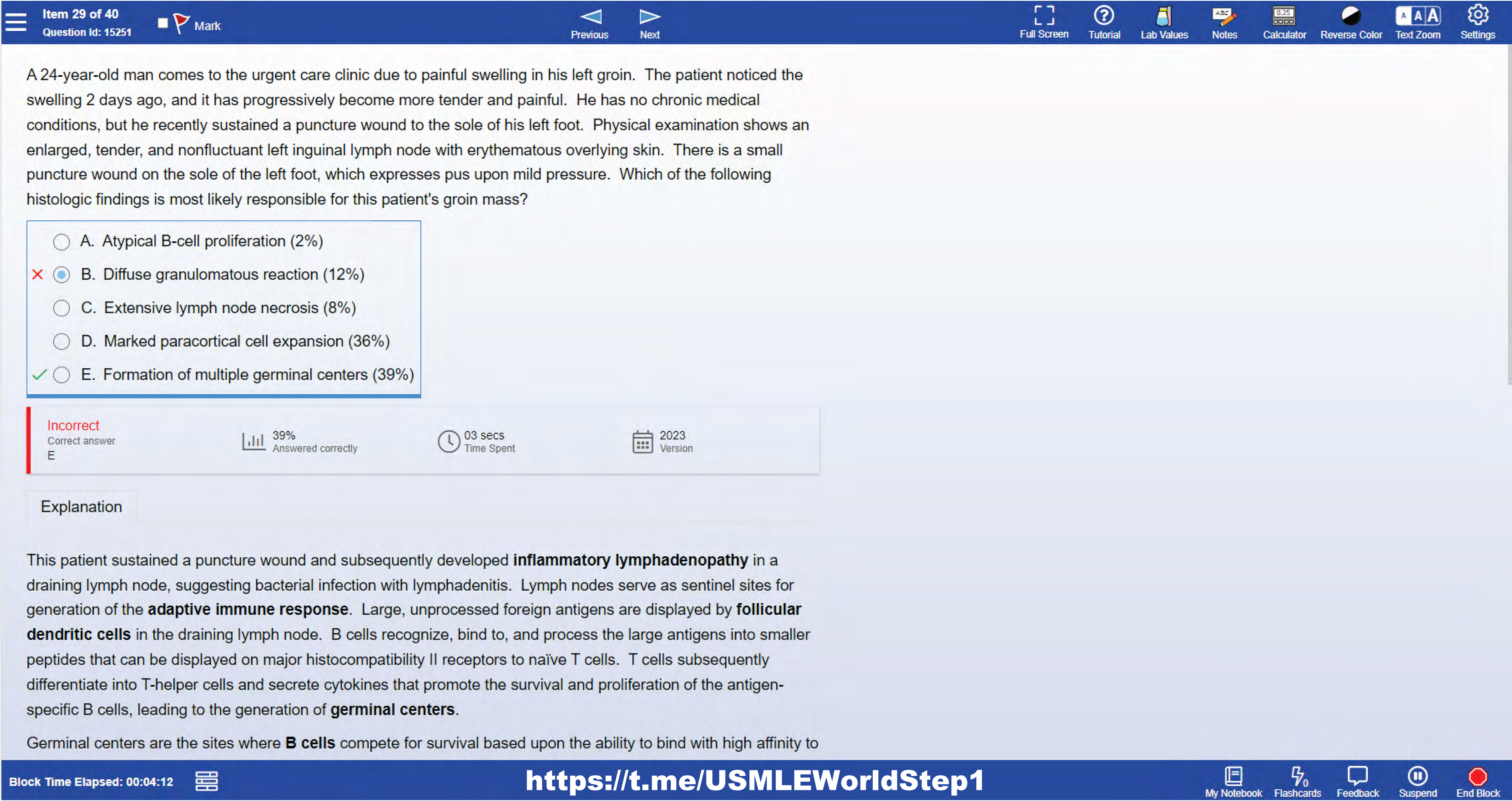

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○ A. Atypical B-cell proliferation (2%)
✗ ● B. Diffuse granulomatous reaction (12%)
○ C. Extensive lymph node necrosis (8%)
○ D. Marked paracortical cell expansion (36%)
✓ ○ E. Formation of multiple germinal centers (39%)

Incorrect
Correct answer
E

39%
Answered correctly

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Explanation

This patient sustained a puncture wound and subsequently developed **inflammatory lymphadenopathy** in a draining lymph node, suggesting bacterial infection with lymphadenitis. Lymph nodes serve as sentinel sites for generation of the **adaptive immune response**. Large, unprocessed foreign antigens are displayed by **follicular dendritic cells** in the draining lymph node. B cells recognize, bind to, and process the large antigens into smaller peptides that can be displayed on major histocompatibility II receptors to naïve T cells. T cells subsequently differentiate into T-helper cells and secrete cytokines that promote the survival and proliferation of the antigen-specific B cells, leading to the generation of **germinal centers**.

Germinal centers are the sites where **B cells** compete for survival based upon the ability to bind with high affinity to

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This patient sustained a puncture wound and subsequently developed **inflammatory lymphadenopathy** in a draining lymph node, suggesting bacterial infection with lymphadenitis. Lymph nodes serve as sentinel sites for generation of the **adaptive immune response**. Large, unprocessed foreign antigens are displayed by **follicular dendritic cells** in the draining lymph node. B cells recognize, bind to, and process the large antigens into smaller peptides that can be displayed on major histocompatibility II receptors to naïve T cells. T cells subsequently differentiate into T-helper cells and secrete cytokines that promote the survival and proliferation of the antigen-specific B cells, leading to the generation of **germinal centers**.

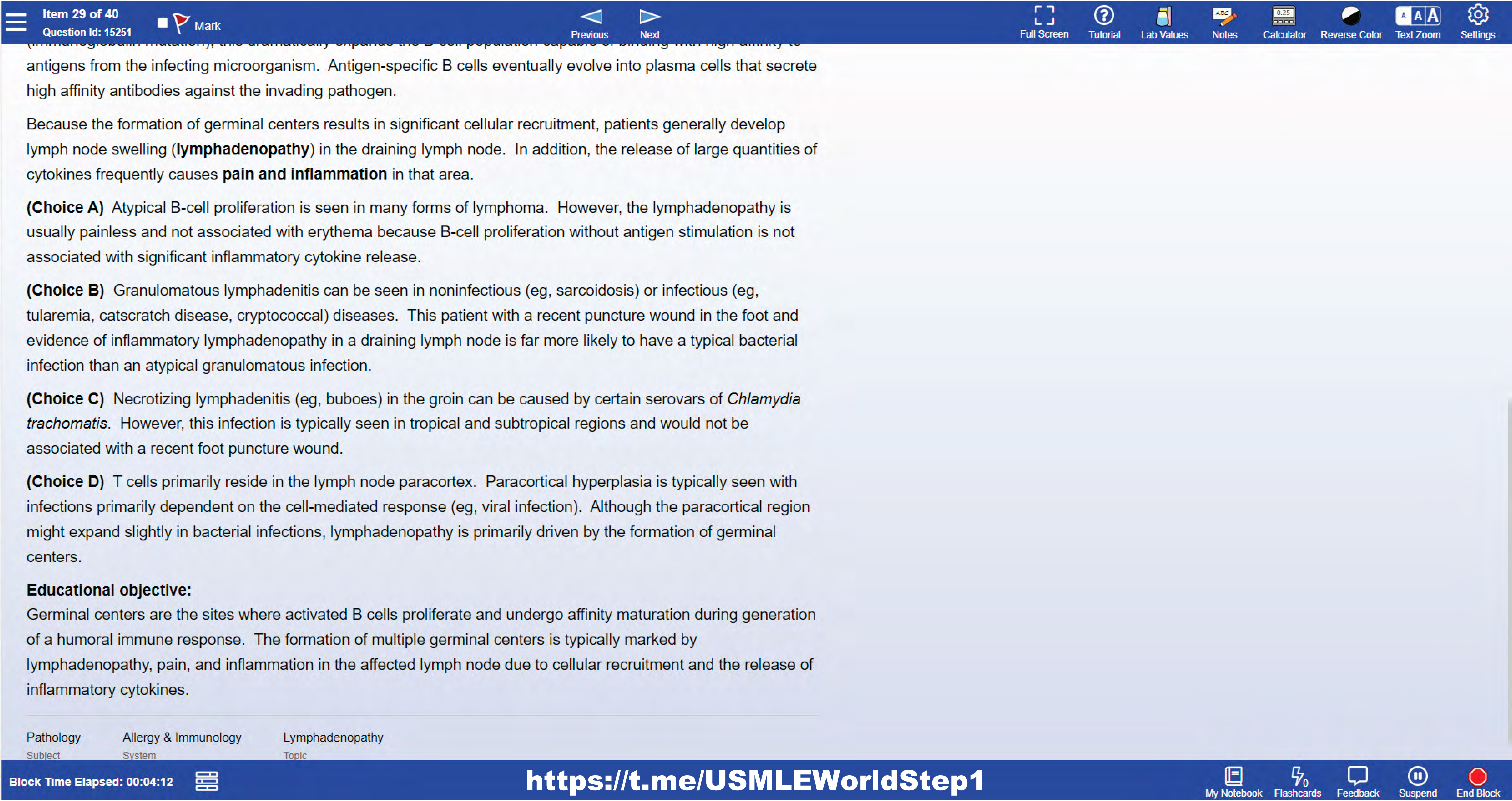
Germinal centers are the sites where **B cells** compete for survival based upon the ability to bind with high affinity to a foreign antigen. Within these regions, B cells rapidly **proliferate** and undergo **somatic hypermutation** (immunoglobulin mutation); this dramatically expands the B cell population capable of binding with high affinity to antigens from the infecting microorganism. Antigen-specific B cells eventually evolve into plasma cells that secrete high affinity antibodies against the invading pathogen.

Because the formation of germinal centers results in significant cellular recruitment, patients generally develop lymph node swelling (**lymphadenopathy**) in the draining lymph node. In addition, the release of large quantities of cytokines frequently causes **pain and inflammation** in that area.

(Choice A) Atypical B-cell proliferation is seen in many forms of lymphoma. However, the lymphadenopathy is usually painless and not associated with erythema because B-cell proliferation without antigen stimulation is not associated with significant inflammatory cytokine release.

(Choice B) Granulomatous lymphadenitis can be seen in noninfectious (eg, sarcoidosis) or infectious (eg, tularemia, catscratch disease, cryptococcal) diseases. This patient with a recent puncture wound in the foot and evidence of inflammatory lymphadenopathy in a draining lymph node is far more likely to have a typical bacterial infection than an atypical granulomatous infection.

(Choice C) Necrotizing lymphadenitis (eg, buboes) in the groin can be caused by certain serovars of *Chlamydia trachomatis*. However, this infection is typically seen in tropical and subtropical regions and would not be



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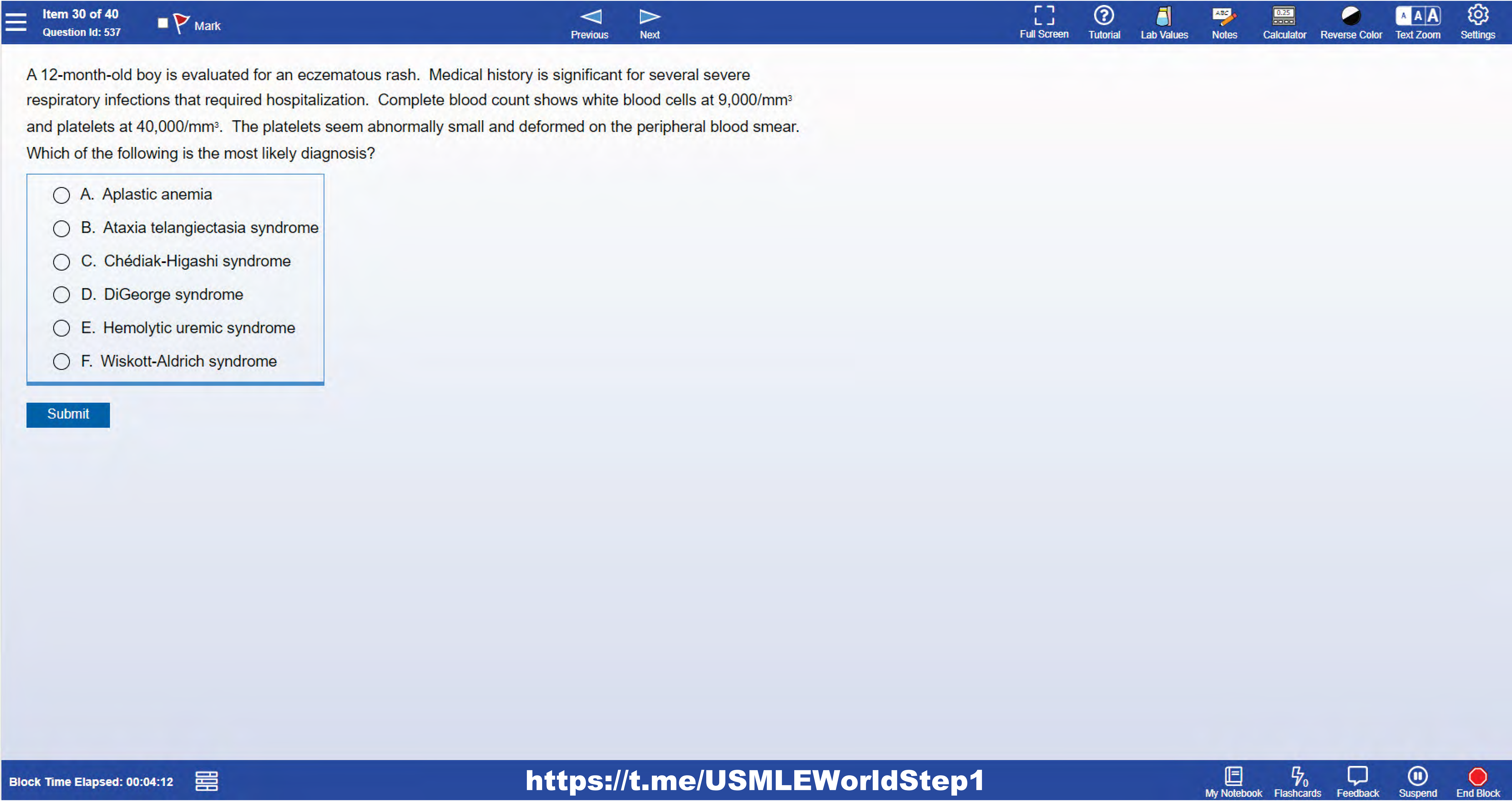
(Choice D) T cells primarily reside in the lymph node paracortex. Paracortical hyperplasia is typically seen with infections primarily dependent on the cell-mediated response (eg, viral infection). Although the paracortical region might expand slightly in bacterial infections, lymphadenopathy is primarily driven by the formation of germinal centers.

Educational objective:
Germinal centers are the sites where activated B cells proliferate and undergo affinity maturation during generation of a humoral immune response. The formation of multiple germinal centers is typically marked by lymphadenopathy, pain, and inflammation in the affected lymph node due to cellular recruitment and the release of inflammatory cytokines.

Pathology	Allergy & Immunology	Lymphadenopathy
Subject	System	Topic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A 12-month-old boy is evaluated for an eczematous rash. Medical history is significant for several severe respiratory infections that required hospitalization. Complete blood count shows white blood cells at 9,000/mm^3 and platelets at 40,000/mm^3. The platelets seem abnormally small and deformed on the peripheral blood smear. Which of the following is the most likely diagnosis?

○ A. Aplastic anemia
○ B. Ataxia telangiectasia syndrome
○ C. Chédiak-Higashi syndrome
○ D. DiGeorge syndrome
○ E. Hemolytic uremic syndrome
○ F. Wiskott-Aldrich syndrome

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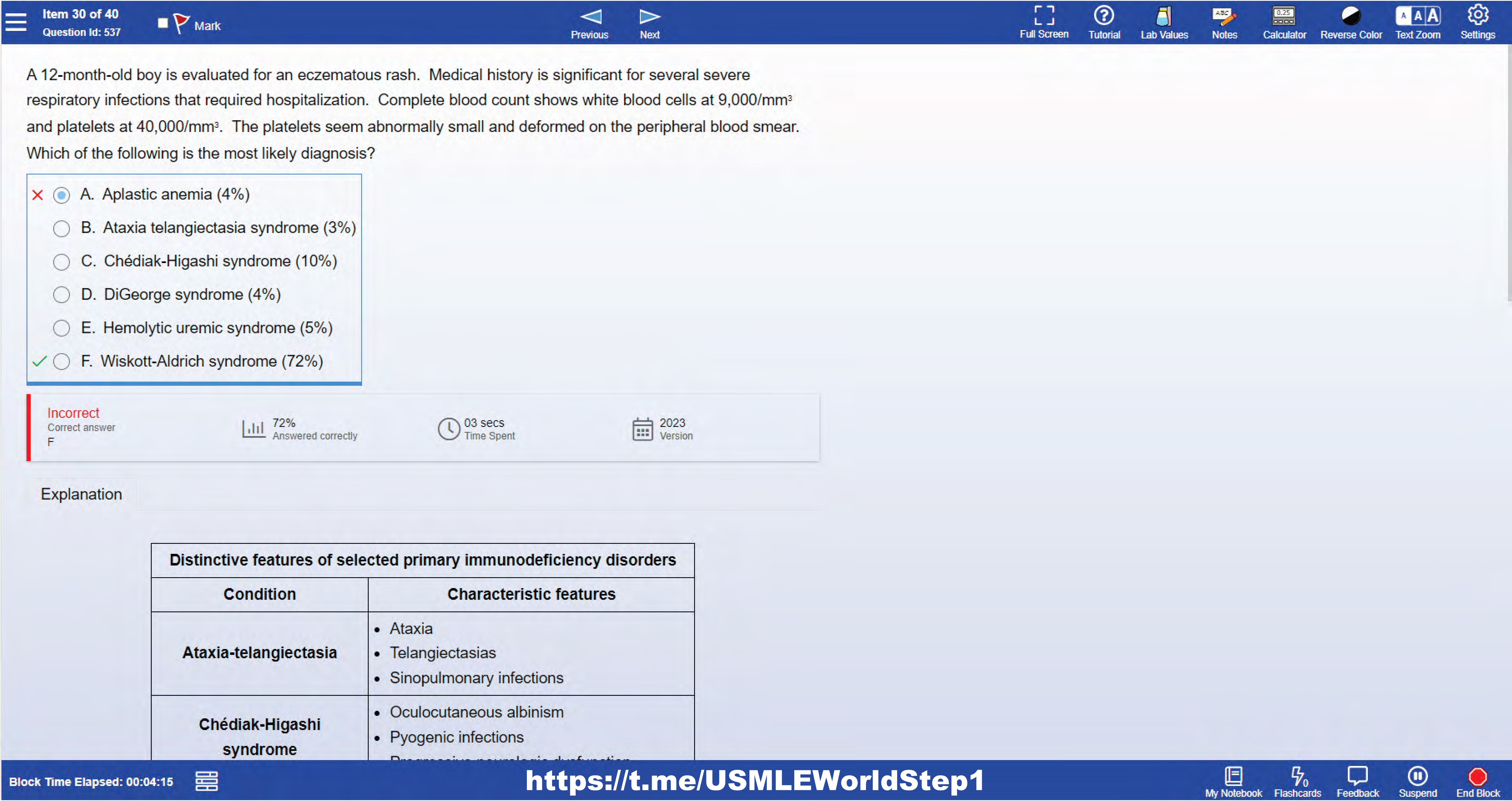
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- ✗ ● A. Aplastic anemia (4%)
- ○ B. Ataxia telangiectasia syndrome (3%)
- ○ C. Chédiak-Higashi syndrome (10%)
- ○ D. DiGeorge syndrome (4%)
- ○ E. Hemolytic uremic syndrome (5%)
- ✓ ○ F. Wiskott-Aldrich syndrome (72%)

Incorrect
Correct answer
F

72%
Answered correctly

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Explanation

Distinctive features of selected primary immunodeficiency disorders

Condition	Characteristic features
Ataxia-telangiectasia	• Ataxia • Telangiectasias • Sinopulmonary infections
Chédiak-Higashi syndrome	• Oculocutaneous albinism • Pyogenic infections • Progressive neurologic dysfunction

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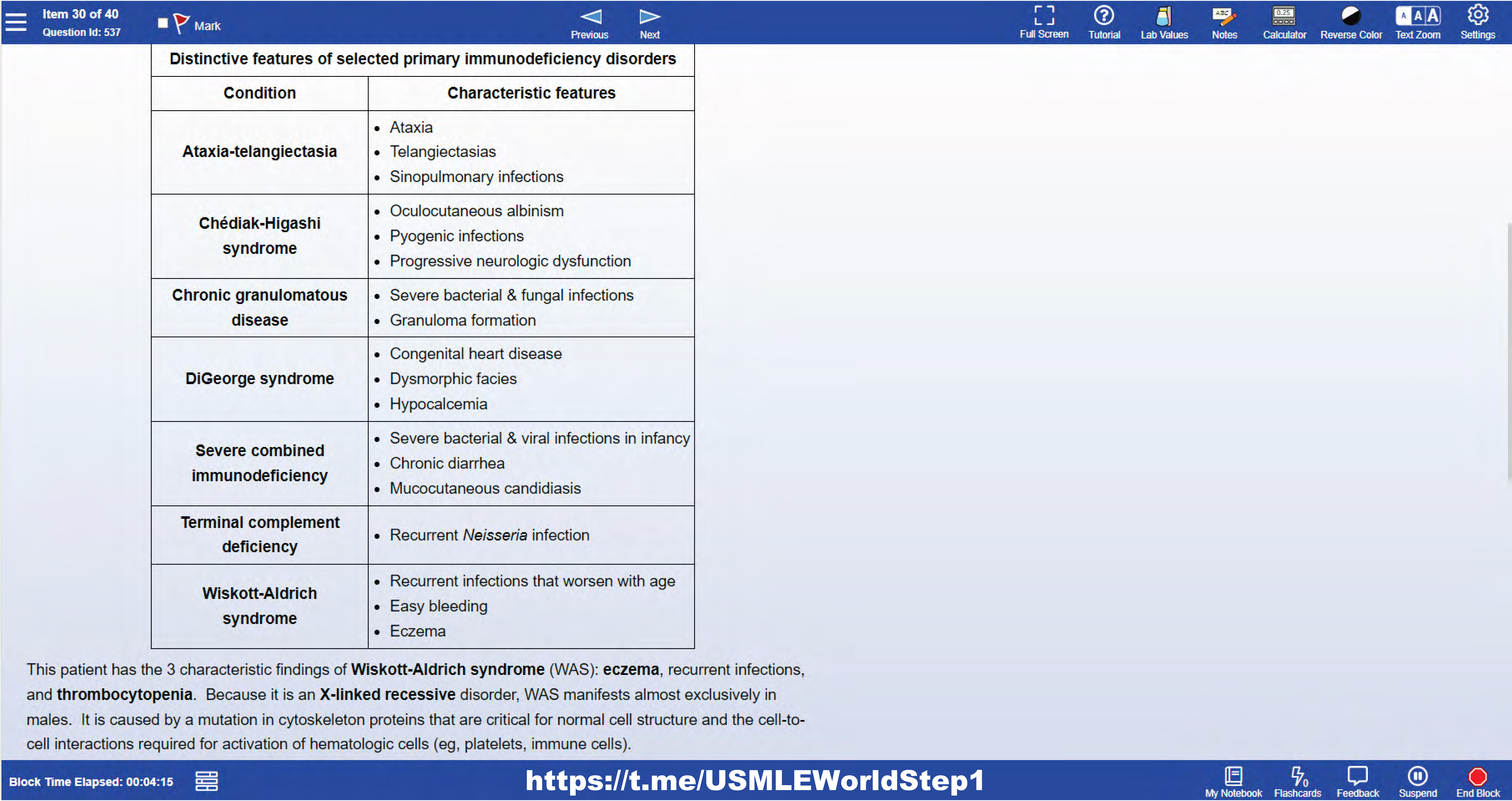
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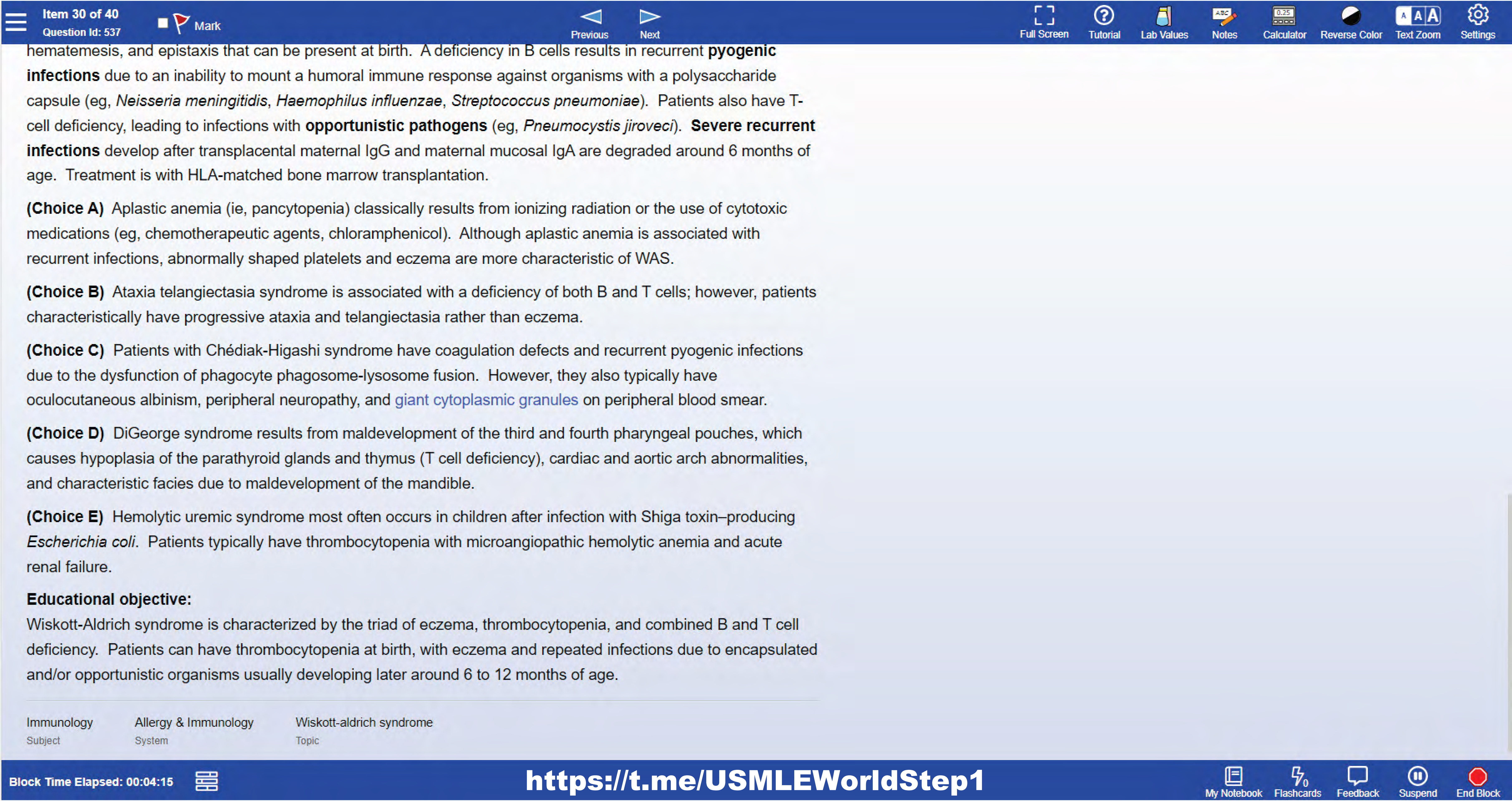
Ataxia-telangiectasia	• Ataxia • Telangiectasias • Sinopulmonary infections
Chédiak-Higashi syndrome	• Oculocutaneous albinism • Pyogenic infections • Progressive neurologic dysfunction
Chronic granulomatous disease	• Severe bacterial & fungal infections • Granuloma formation
DiGeorge syndrome	• Congenital heart disease • Dysmorphic facies • Hypocalcemia
Severe combined immunodeficiency	• Severe bacterial & viral infections in infancy • Chronic diarrhea • Mucocutaneous candidiasis
Terminal complement deficiency	• Recurrent *Neisseria* infection
Wiskott-Aldrich syndrome	• Recurrent infections that worsen with age • Easy bleeding • Eczema

This patient has the 3 characteristic findings of **Wiskott-Aldrich syndrome** (WAS): **eczema**, recurrent infections, and **thrombocytopenia**. Because it is an **X-linked recessive** disorder, WAS manifests almost exclusively in males. It is caused by a mutation in cytoskeleton proteins that are critical for normal cell structure and the cell-to-cell interactions required for activation of hematologic cells (eg, platelets, immune cells).



hematemesis, and epistaxis that can be present at birth. A deficiency in B cells results in recurrent **pyogenic infections** due to an inability to mount a humoral immune response against organisms with a polysaccharide capsule (eg, *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*). Patients also have T-cell deficiency, leading to infections with **opportunistic pathogens** (eg, *Pneumocystis jiroveci*). **Severe recurrent infections** develop after transplacental maternal IgG and maternal mucosal IgA are degraded around 6 months of age. Treatment is with HLA-matched bone marrow transplantation.

(Choice A) Aplastic anemia (ie, pancytopenia) classically results from ionizing radiation or the use of cytotoxic medications (eg, chemotherapeutic agents, chloramphenicol). Although aplastic anemia is associated with recurrent infections, abnormally shaped platelets and eczema are more characteristic of WAS.

(Choice B) Ataxia telangiectasia syndrome is associated with a deficiency of both B and T cells; however, patients characteristically have progressive ataxia and telangiectasia rather than eczema.

(Choice C) Patients with Chédiak-Higashi syndrome have coagulation defects and recurrent pyogenic infections due to the dysfunction of phagocyte phagosome-lysosome fusion. However, they also typically have oculocutaneous albinism, peripheral neuropathy, and giant cytoplasmic granules on peripheral blood smear.

(Choice D) DiGeorge syndrome results from maldevelopment of the third and fourth pharyngeal pouches, which causes hypoplasia of the parathyroid glands and thymus (T cell deficiency), cardiac and aortic arch abnormalities, and characteristic facies due to maldevelopment of the mandible.

(Choice E) Hemolytic uremic syndrome most often occurs in children after infection with Shiga toxin–producing *Escherichia coli*. Patients typically have thrombocytopenia with microangiopathic hemolytic anemia and acute renal failure.

Educational objective:

Wiskott-Aldrich syndrome is characterized by the triad of eczema, thrombocytopenia, and combined B and T cell deficiency. Patients can have thrombocytopenia at birth, with eczema and repeated infections due to encapsulated and/or opportunistic organisms usually developing later around 6 to 12 months of age.

Immunology	Allergy & Immunology	Wiskott-aldrich syndrome
Subject	System	Topic

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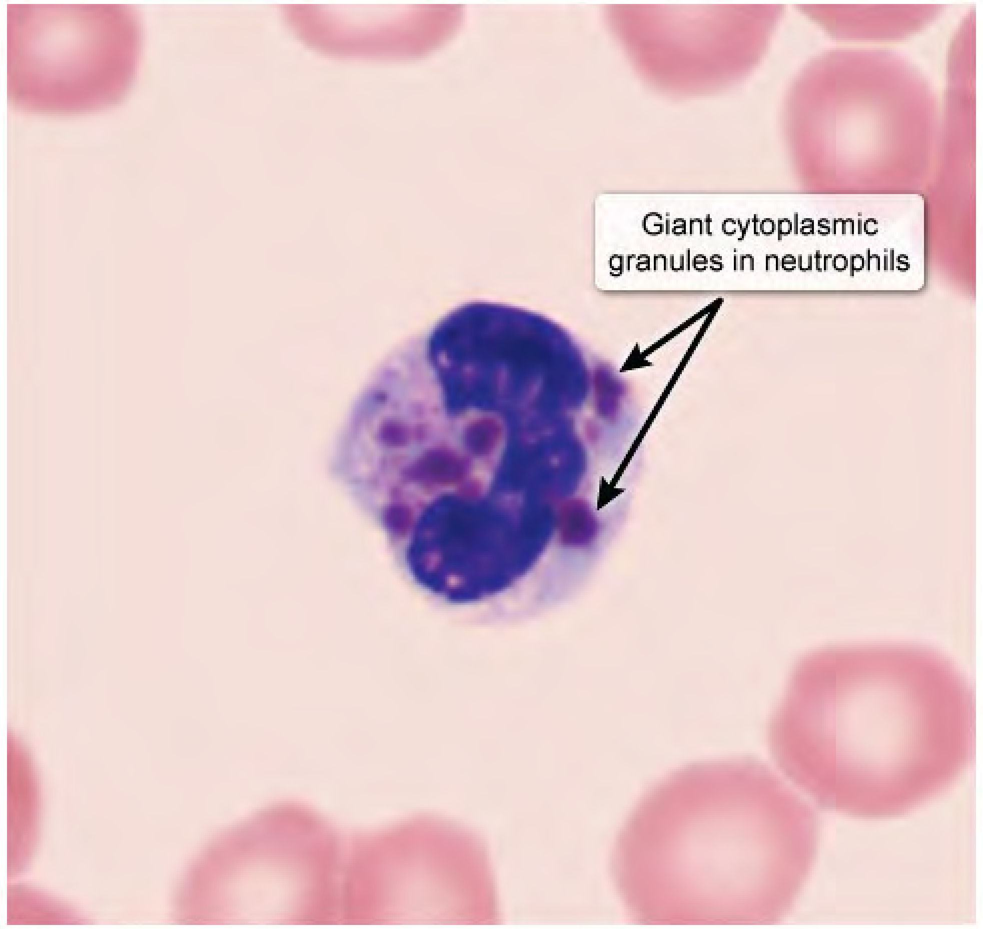
Chédiak-Higashi syndrome



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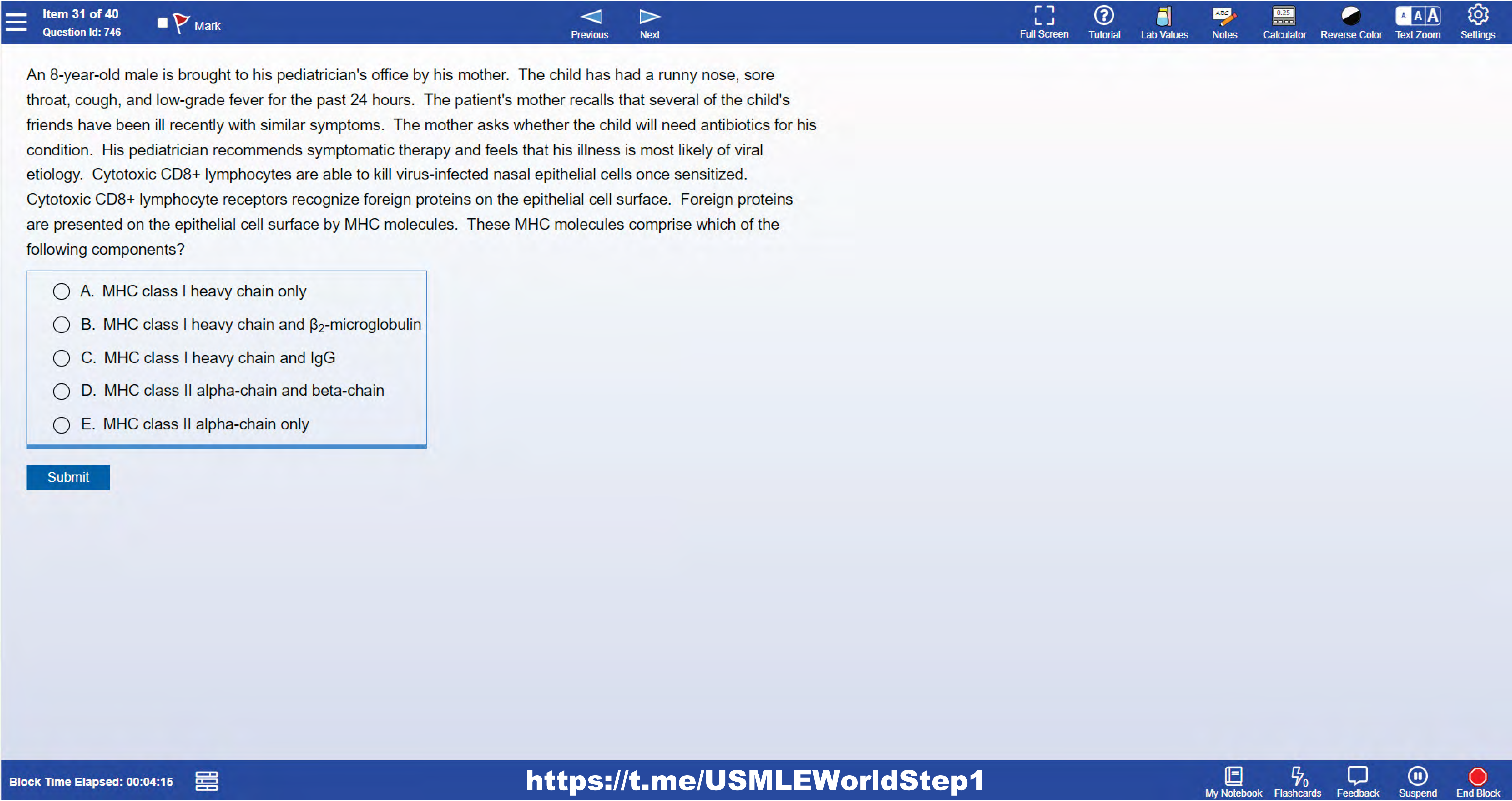
Immunology	Allergy & Immunology	Wiskott-aldrich syndrome
Subject	System	Topic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An 8-year-old male is brought to his pediatrician's office by his mother. The child has had a runny nose, sore throat, cough, and low-grade fever for the past 24 hours. The patient's mother recalls that several of the child's friends have been ill recently with similar symptoms. The mother asks whether the child will need antibiotics for his condition. His pediatrician recommends symptomatic therapy and feels that his illness is most likely of viral etiology. Cytotoxic CD8+ lymphocytes are able to kill virus-infected nasal epithelial cells once sensitized. Cytotoxic CD8+ lymphocyte receptors recognize foreign proteins on the epithelial cell surface. Foreign proteins are presented on the epithelial cell surface by MHC molecules. These MHC molecules comprise which of the following components?

- ○ A. MHC class I heavy chain only
- ○ B. MHC class I heavy chain and β_2-microglobulin
- ○ C. MHC class I heavy chain and IgG
- ○ D. MHC class II alpha-chain and beta-chain
- ○ E. MHC class II alpha-chain only

Submit

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✗ ● A. MHC class I heavy chain only (17%)
✓ ○ B. MHC class I heavy chain and β_2-microglobulin (65%)
○ C. MHC class I heavy chain and IgG (7%)
○ D. MHC class II alpha-chain and beta-chain (6%)
○ E. MHC class II alpha-chain only (2%)

Incorrect
Correct answer
B

65%
Answered correctly

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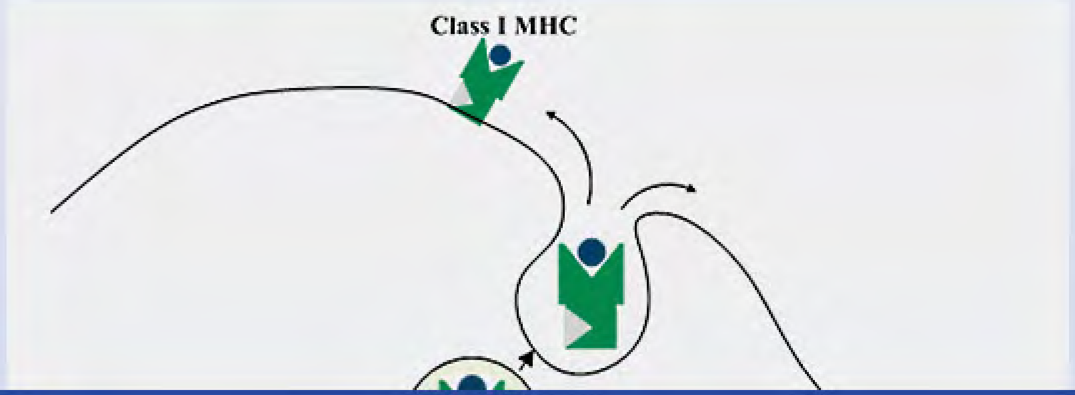
Explanation



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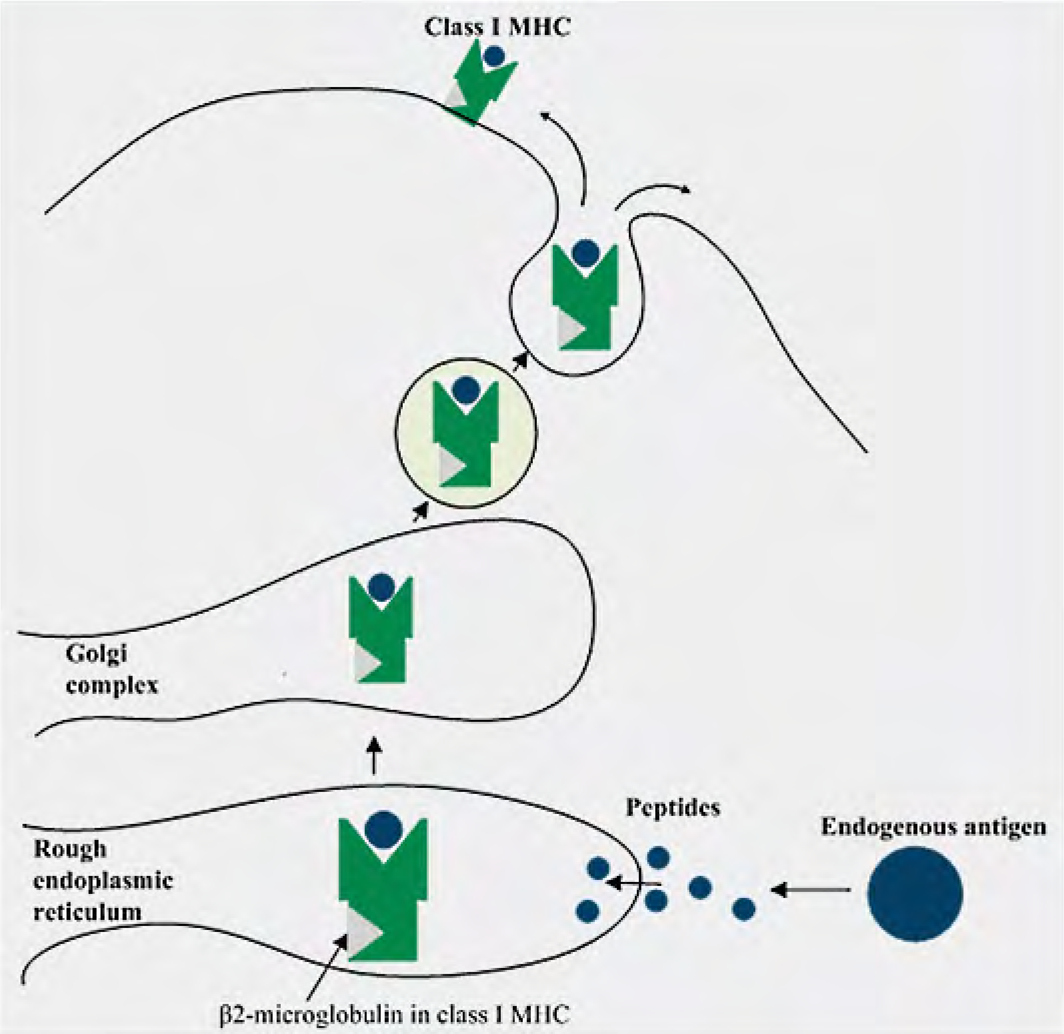
Class I MHC
Golgi complex
Peptides
Endogenous antigen
Rough endoplasmic reticulum
β2-microglobulin in class I MHC

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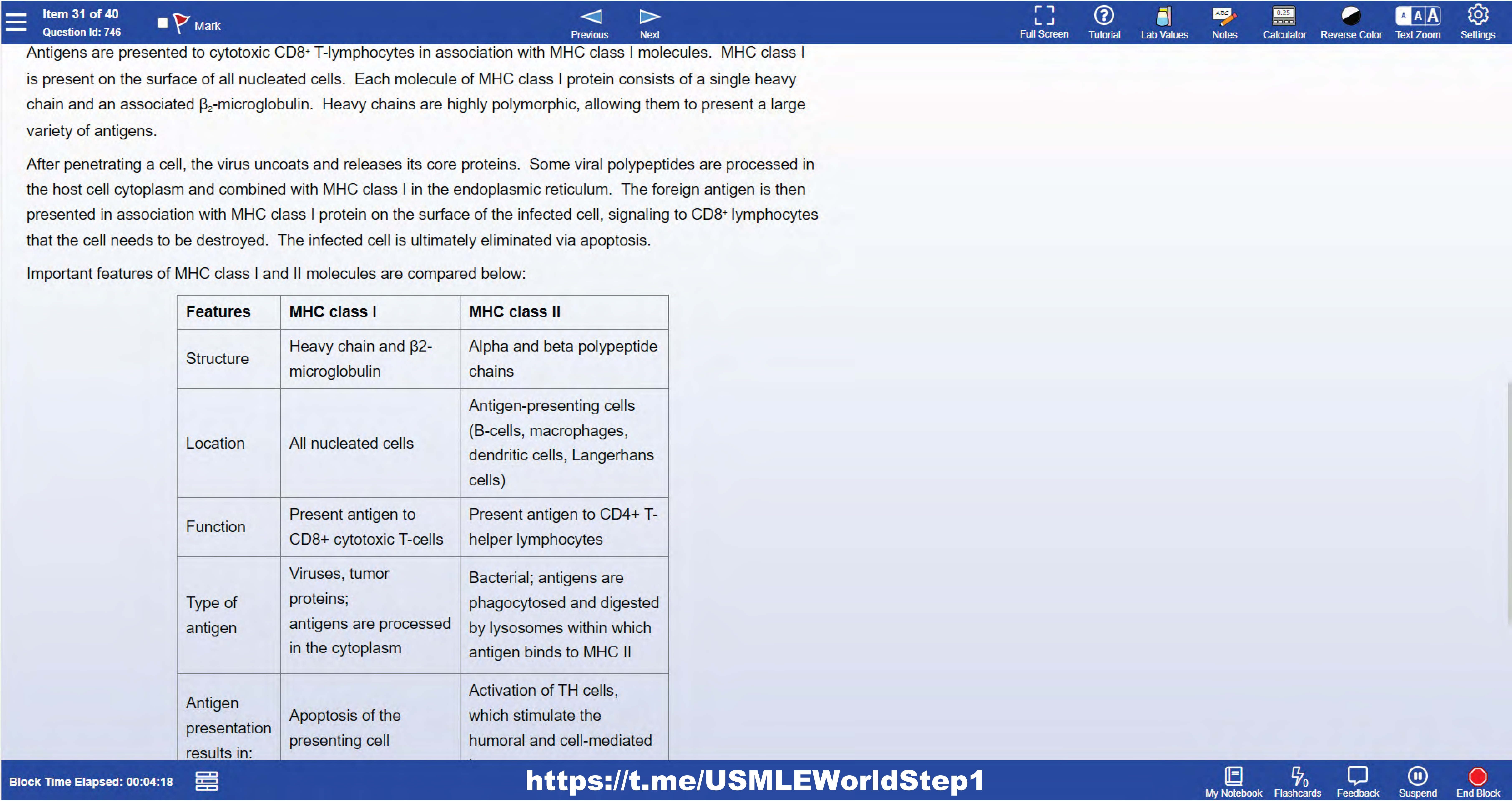
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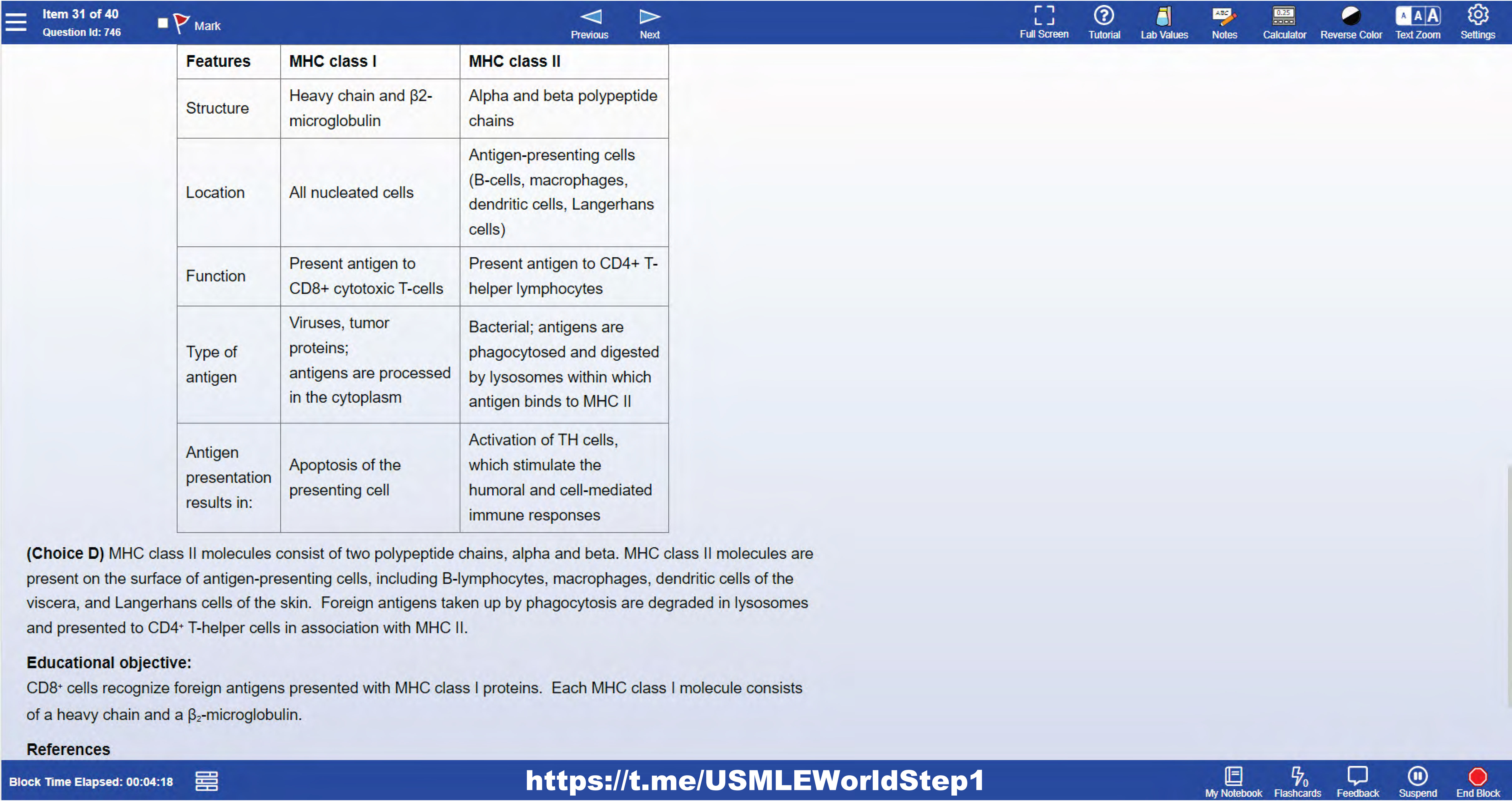
Antigens are presented to cytotoxic $CD8^+$ T-lymphocytes in association with MHC class I molecules. MHC class I is present on the surface of all nucleated cells. Each molecule of MHC class I protein consists of a single heavy chain and an associated β_2-microglobulin. Heavy chains are highly polymorphic, allowing them to present a large variety of antigens.

After penetrating a cell, the virus uncoats and releases its core proteins. Some viral polypeptides are processed in the host cell cytoplasm and combined with MHC class I in the endoplasmic reticulum. The foreign antigen is then presented in association with MHC class I protein on the surface of the infected cell, signaling to $CD8^+$ lymphocytes that the cell needs to be destroyed. The infected cell is ultimately eliminated via apoptosis.

Important features of MHC class I and II molecules are compared below:

Features	**MHC class I**	**MHC class II**
Structure	Heavy chain and β2-microglobulin	Alpha and beta polypeptide chains
Location	All nucleated cells	Antigen-presenting cells (B-cells, macrophages, dendritic cells, Langerhans cells)
Function	Present antigen to CD8+ cytotoxic T-cells	Present antigen to CD4+ T-helper lymphocytes
Type of antigen	Viruses, tumor proteins; antigens are processed in the cytoplasm	Bacterial; antigens are phagocytosed and digested by lysosomes within which antigen binds to MHC II
Antigen presentation results in:	Apoptosis of the presenting cell	Activation of TH cells, which stimulate the humoral and cell-mediated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Antigen presentation results in:	Apoptosis of the presenting cell	Activation of TH cells, which stimulate the humoral and cell-mediated immune responses

(Choice D) MHC class II molecules consist of two polypeptide chains, alpha and beta. MHC class II molecules are present on the surface of antigen-presenting cells, including B-lymphocytes, macrophages, dendritic cells of the viscera, and Langerhans cells of the skin. Foreign antigens taken up by phagocytosis are degraded in lysosomes and presented to $CD4^+$ T-helper cells in association with MHC II.

Educational objective:

$CD8^+$ cells recognize foreign antigens presented with MHC class I proteins. Each MHC class I molecule consists of a heavy chain and a β_2-microglobulin.

References

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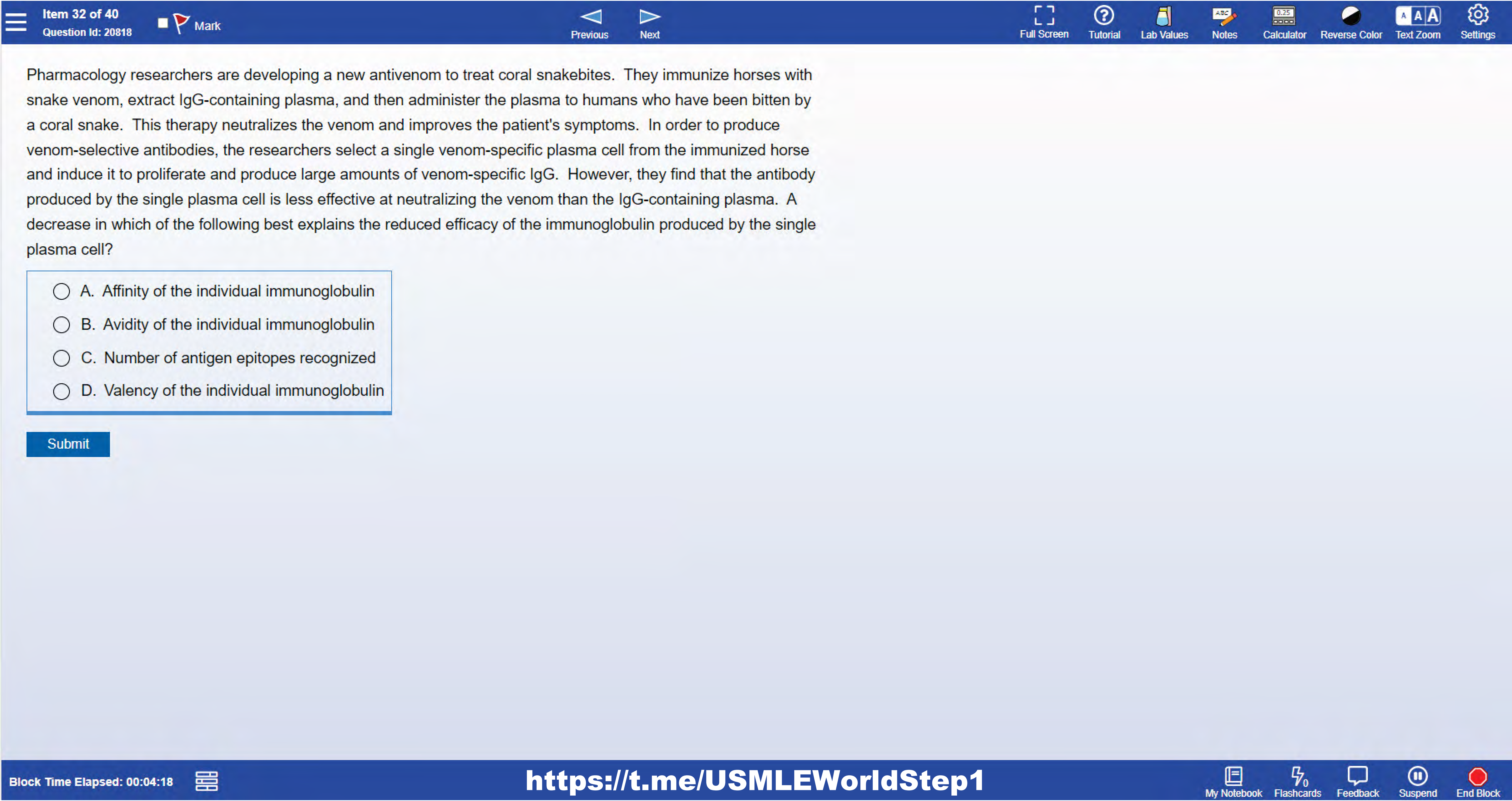
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Pharmacology researchers are developing a new antivenom to treat coral snakebites. They immunize horses with snake venom, extract IgG-containing plasma, and then administer the plasma to humans who have been bitten by a coral snake. This therapy neutralizes the venom and improves the patient's symptoms. In order to produce venom-selective antibodies, the researchers select a single venom-specific plasma cell from the immunized horse and induce it to proliferate and produce large amounts of venom-specific IgG. However, they find that the antibody produced by the single plasma cell is less effective at neutralizing the venom than the IgG-containing plasma. A decrease in which of the following best explains the reduced efficacy of the immunoglobulin produced by the single plasma cell?

- ○ A. Affinity of the individual immunoglobulin
- ○ B. Avidity of the individual immunoglobulin
- ○ C. Number of antigen epitopes recognized
- ○ D. Valency of the individual immunoglobulin

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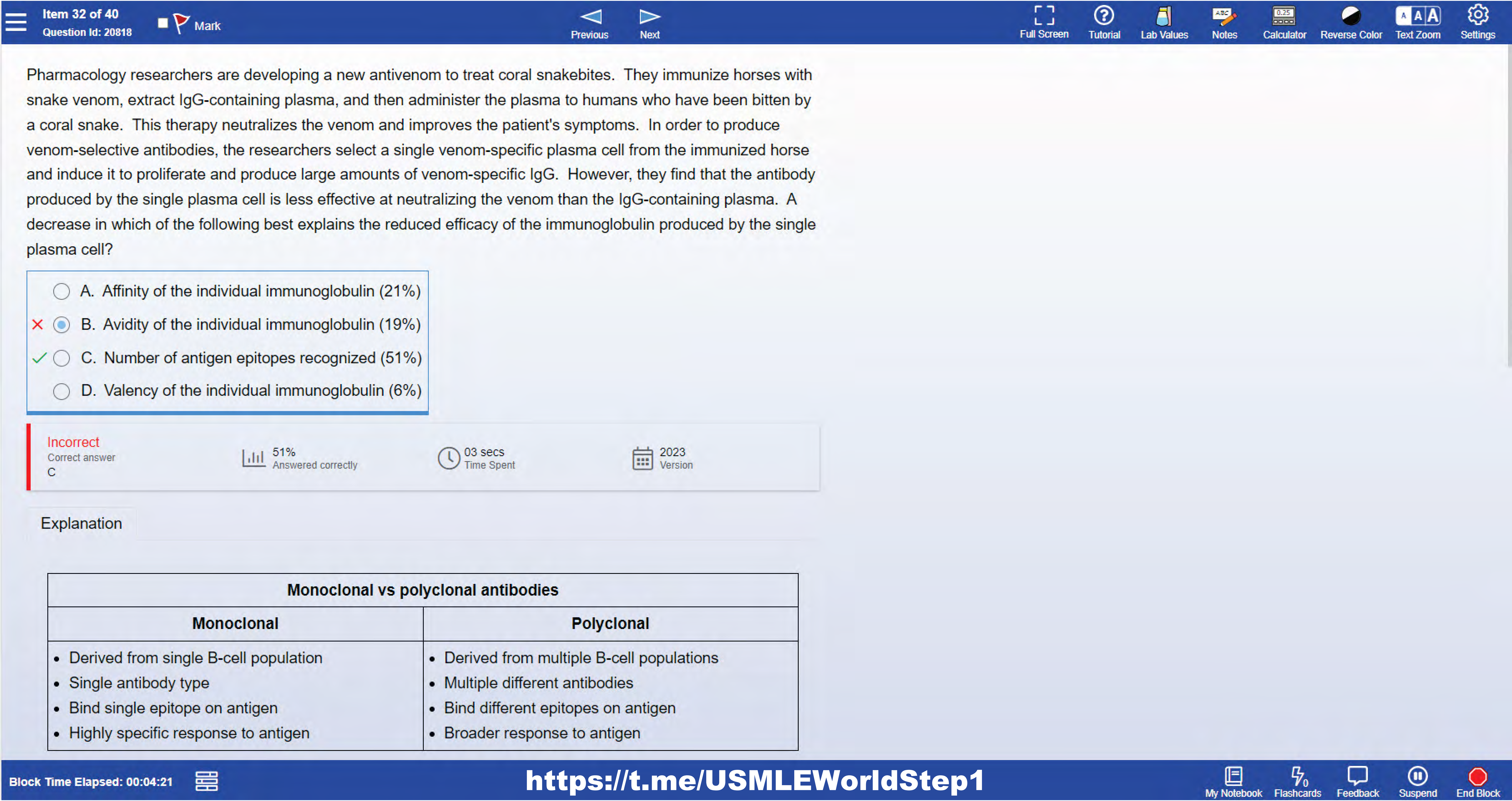
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○ A. Affinity of the individual immunoglobulin (21%)

✗ ● B. Avidity of the individual immunoglobulin (19%)

✓ ○ C. Number of antigen epitopes recognized (51%)

○ D. Valency of the individual immunoglobulin (6%)

Incorrect
Correct answer
C

51%
Answered correctly

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Explanation

Monoclonal vs polyclonal antibodies	
Monoclonal	**Polyclonal**
• Derived from single B-cell population • Single antibody type • Bind single epitope on antigen • Highly specific response to antigen	• Derived from multiple B-cell populations • Multiple different antibodies • Bind different epitopes on antigen • Broader response to antigen

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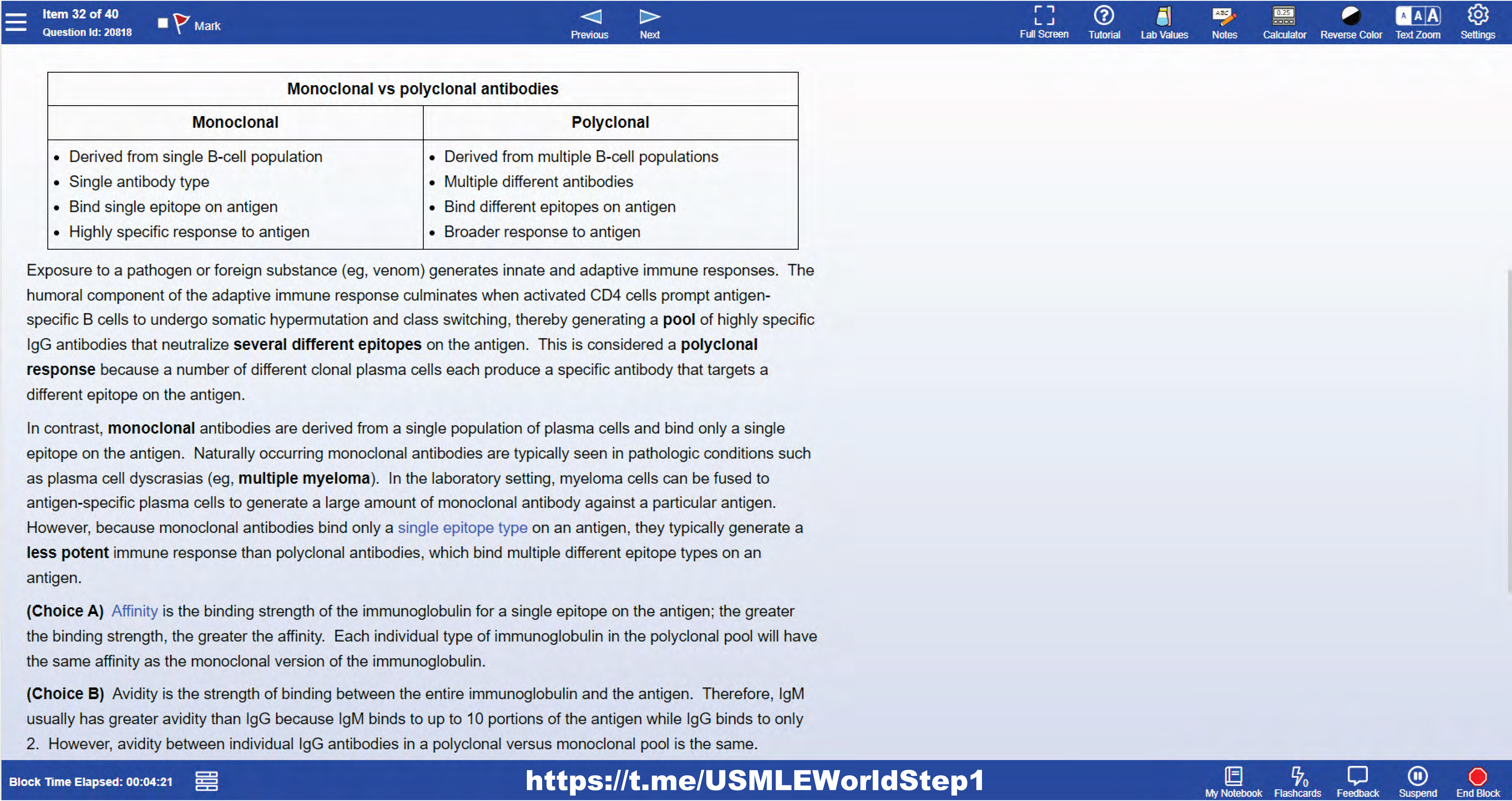

Monoclonal vs polyclonal antibodies	
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Exposure to a pathogen or foreign substance (eg, venom) generates innate and adaptive immune responses. The humoral component of the adaptive immune response culminates when activated CD4 cells prompt antigen-specific B cells to undergo somatic hypermutation and class switching, thereby generating a **pool** of highly specific IgG antibodies that neutralize **several different epitopes** on the antigen. This is considered a **polyclonal response** because a number of different clonal plasma cells each produce a specific antibody that targets a different epitope on the antigen.

In contrast, **monoclonal** antibodies are derived from a single population of plasma cells and bind only a single epitope on the antigen. Naturally occurring monoclonal antibodies are typically seen in pathologic conditions such as plasma cell dyscrasias (eg, **multiple myeloma**). In the laboratory setting, myeloma cells can be fused to antigen-specific plasma cells to generate a large amount of monoclonal antibody against a particular antigen. However, because monoclonal antibodies bind only a single epitope type on an antigen, they typically generate a **less potent** immune response than polyclonal antibodies, which bind multiple different epitope types on an antigen.

(Choice A) Affinity is the binding strength of the immunoglobulin for a single epitope on the antigen; the greater the binding strength, the greater the affinity. Each individual type of immunoglobulin in the polyclonal pool will have the same affinity as the monoclonal version of the immunoglobulin.

(Choice B) Avidity is the strength of binding between the entire immunoglobulin and the antigen. Therefore, IgM usually has greater avidity than IgG because IgM binds to up to 10 portions of the antigen while IgG binds to only 2. However, avidity between individual IgG antibodies in a polyclonal versus monoclonal pool is the same.

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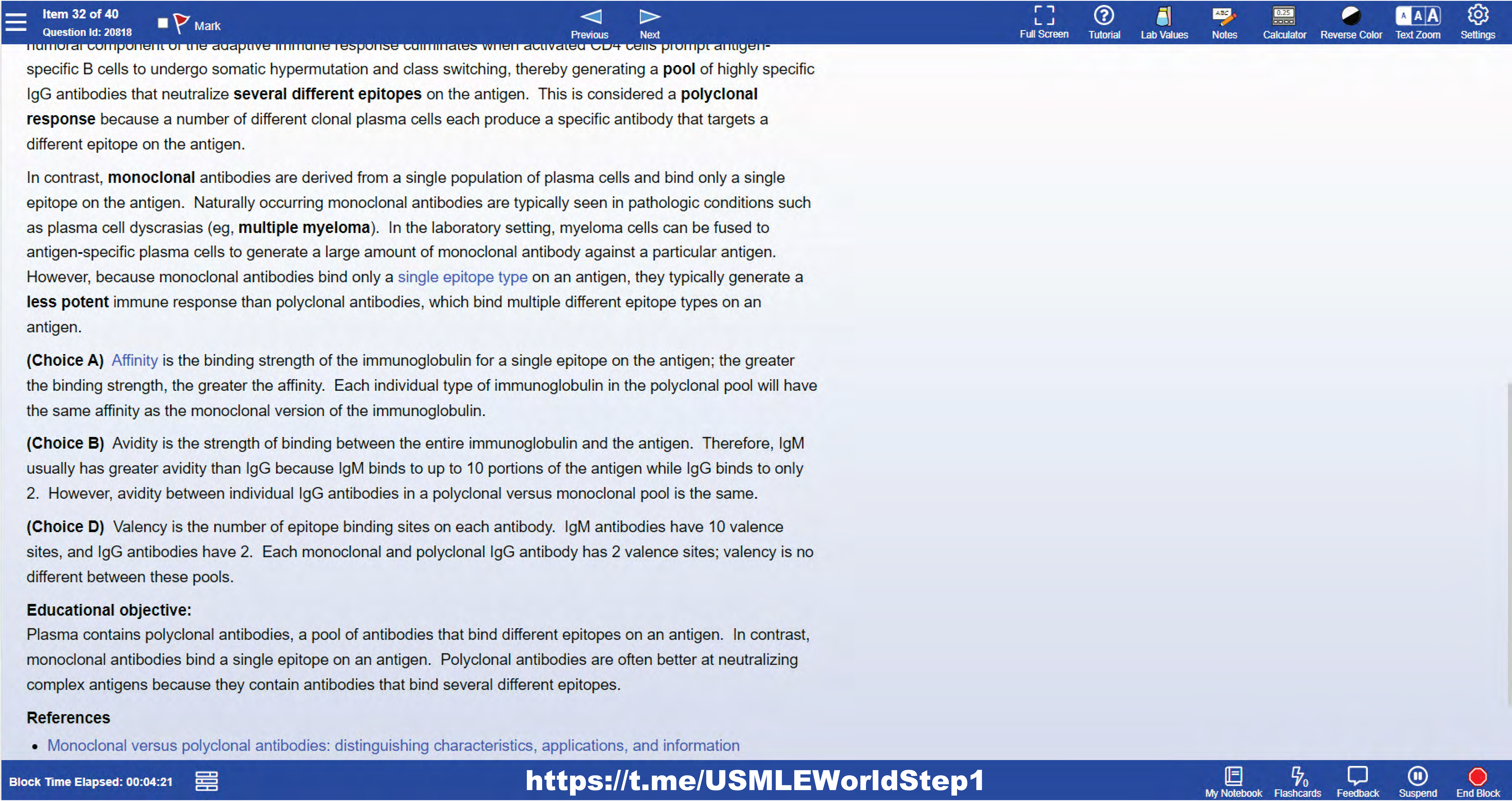

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(Choice D) Valency is the number of epitope binding sites on each antibody. IgM antibodies have 10 valence sites, and IgG antibodies have 2. Each monoclonal and polyclonal IgG antibody has 2 valence sites; valency is no different between these pools.

Educational objective:
Plasma contains polyclonal antibodies, a pool of antibodies that bind different epitopes on an antigen. In contrast, monoclonal antibodies bind a single epitope on an antigen. Polyclonal antibodies are often better at neutralizing complex antigens because they contain antibodies that bind several different epitopes.

References

- Monoclonal versus polyclonal antibodies: distinguishing characteristics, applications, and information

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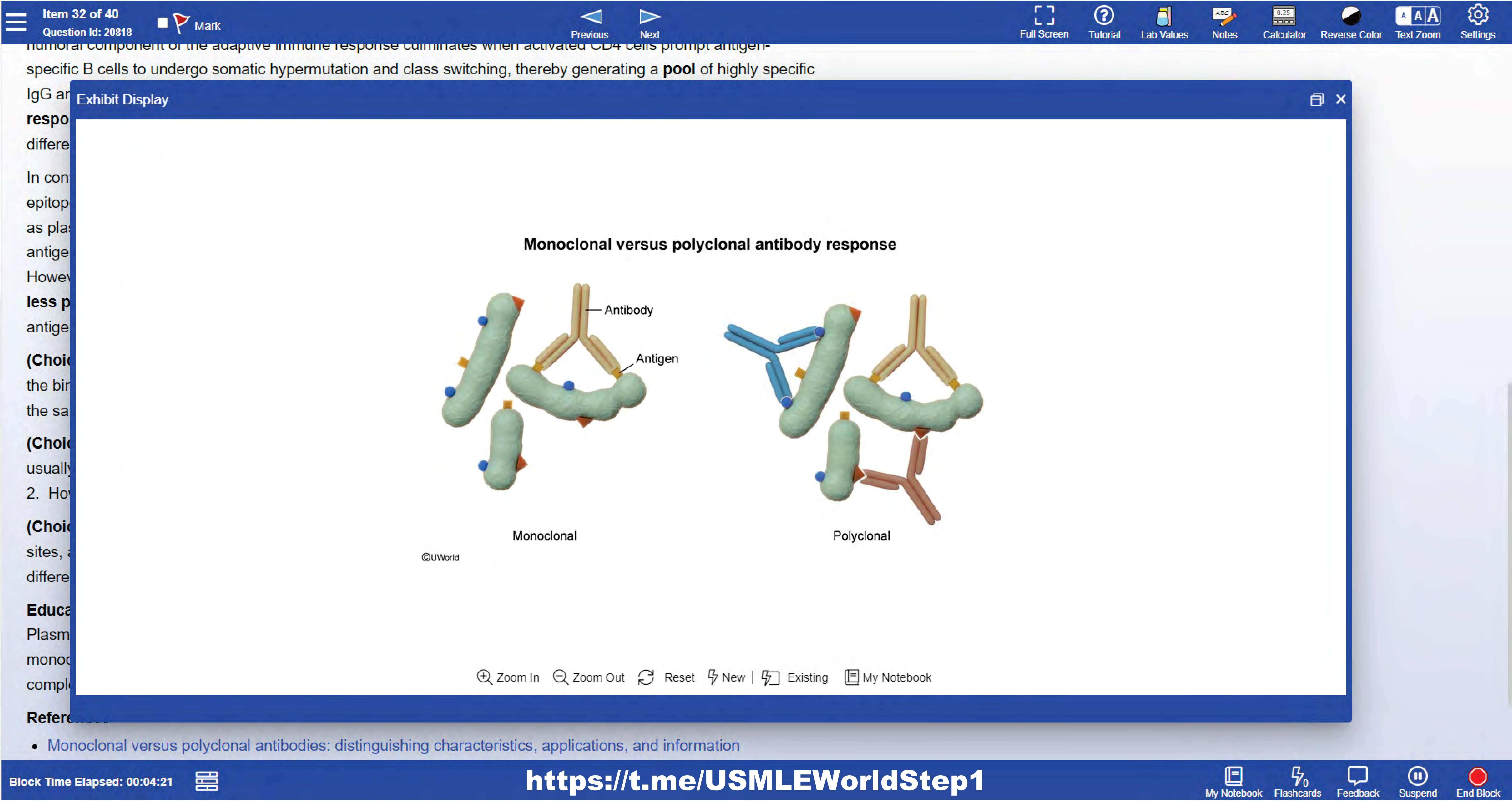
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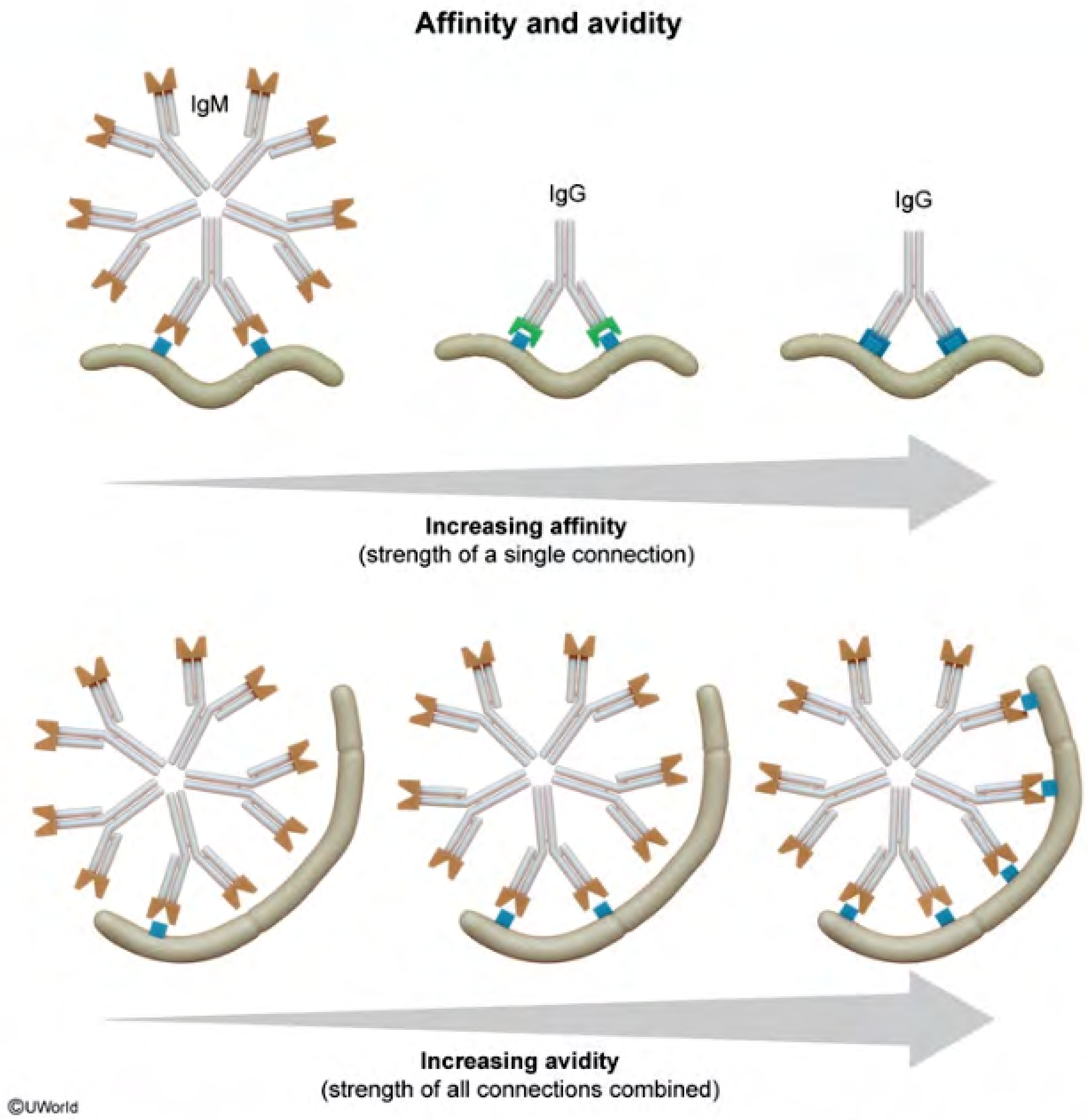

Affinity and avidity

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(strength of a single connection)
Increasing avidity
(strength of all connections combined)
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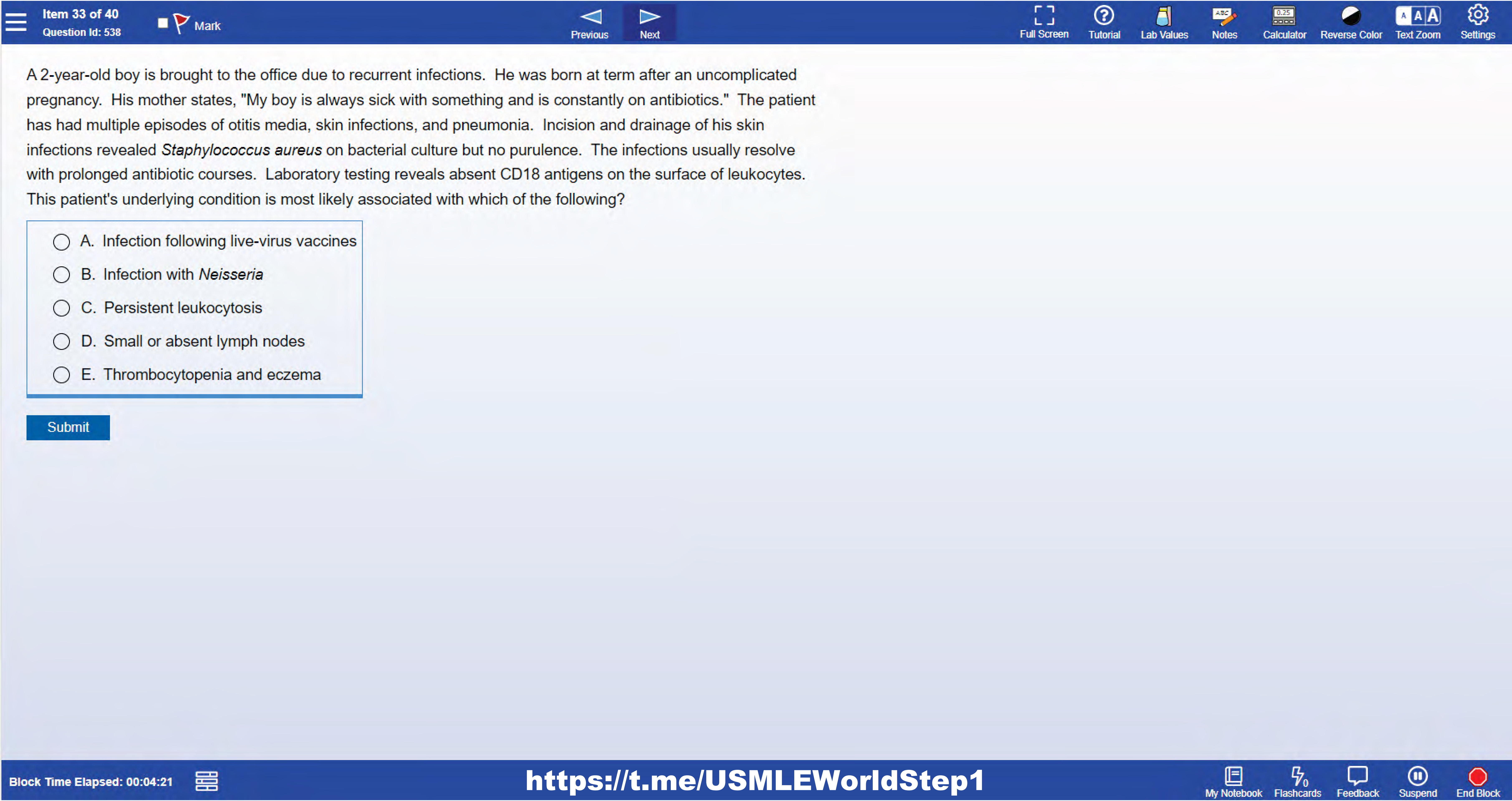
- Monoclonal versus polyclonal antibodies: distinguishing characteristics, applications, and information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A 2-year-old boy is brought to the office due to recurrent infections. He was born at term after an uncomplicated pregnancy. His mother states, "My boy is always sick with something and is constantly on antibiotics." The patient has had multiple episodes of otitis media, skin infections, and pneumonia. Incision and drainage of his skin infections revealed *Staphylococcus aureus* on bacterial culture but no purulence. The infections usually resolve with prolonged antibiotic courses. Laboratory testing reveals absent CD18 antigens on the surface of leukocytes. This patient's underlying condition is most likely associated with which of the following?

○ A. Infection following live-virus vaccines
○ B. Infection with *Neisseria*
○ C. Persistent leukocytosis
○ D. Small or absent lymph nodes
○ E. Thrombocytopenia and eczema

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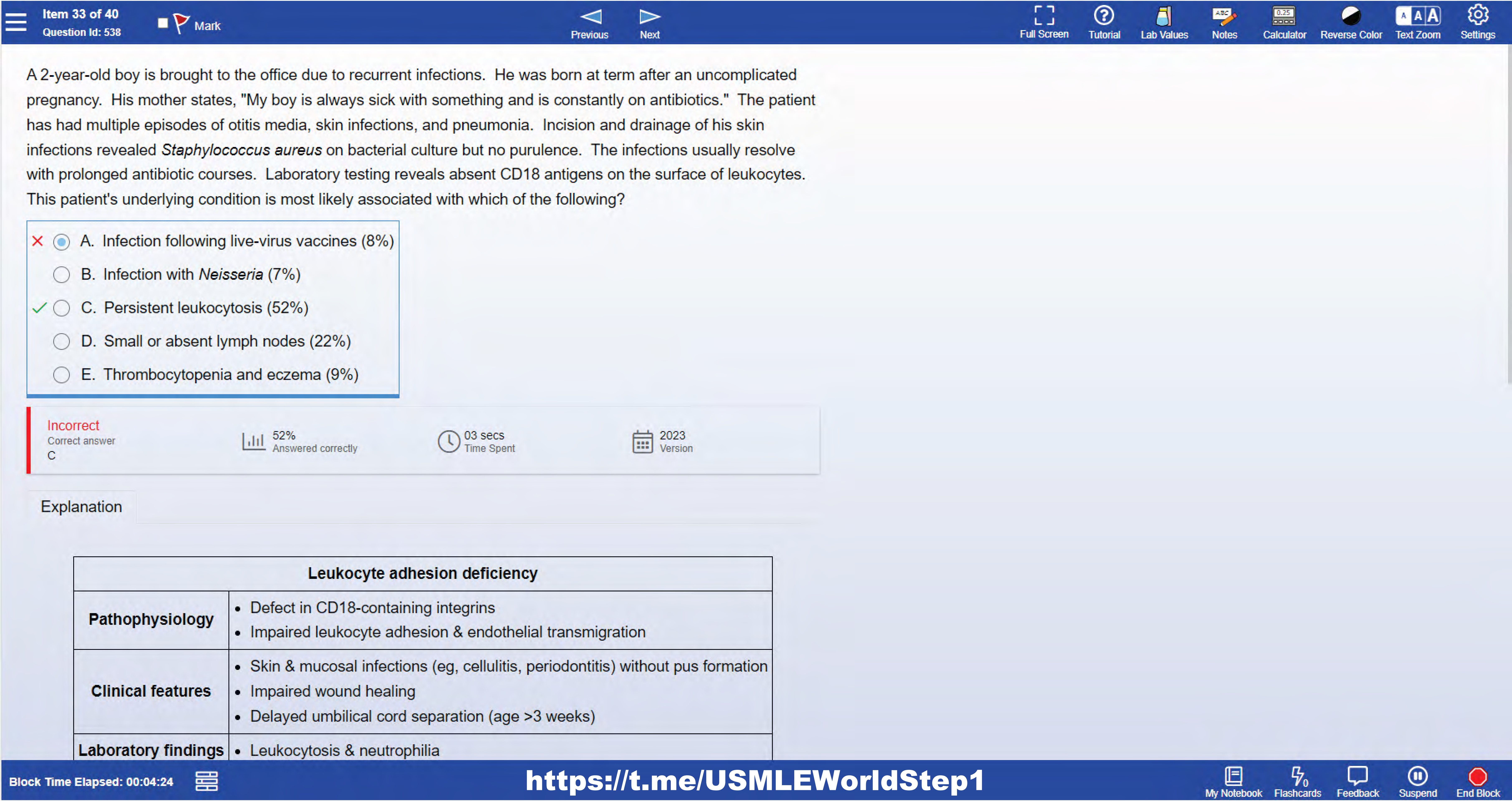
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- ✗ ● A. Infection following live-virus vaccines (8%)
- ○ B. Infection with *Neisseria* (7%)
- ✓ ○ C. Persistent leukocytosis (52%)
- ○ D. Small or absent lymph nodes (22%)
- ○ E. Thrombocytopenia and eczema (9%)

Incorrect
Correct answer
C

52%
Answered correctly

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Explanation

Leukocyte adhesion deficiency	
Pathophysiology	• Defect in CD18-containing integrins • Impaired leukocyte adhesion & endothelial transmigration
Clinical features	• Skin & mucosal infections (eg, cellulitis, periodontitis) without pus formation • Impaired wound healing • Delayed umbilical cord separation (age >3 weeks)
Laboratory findings	• Leukocytosis & neutrophilia

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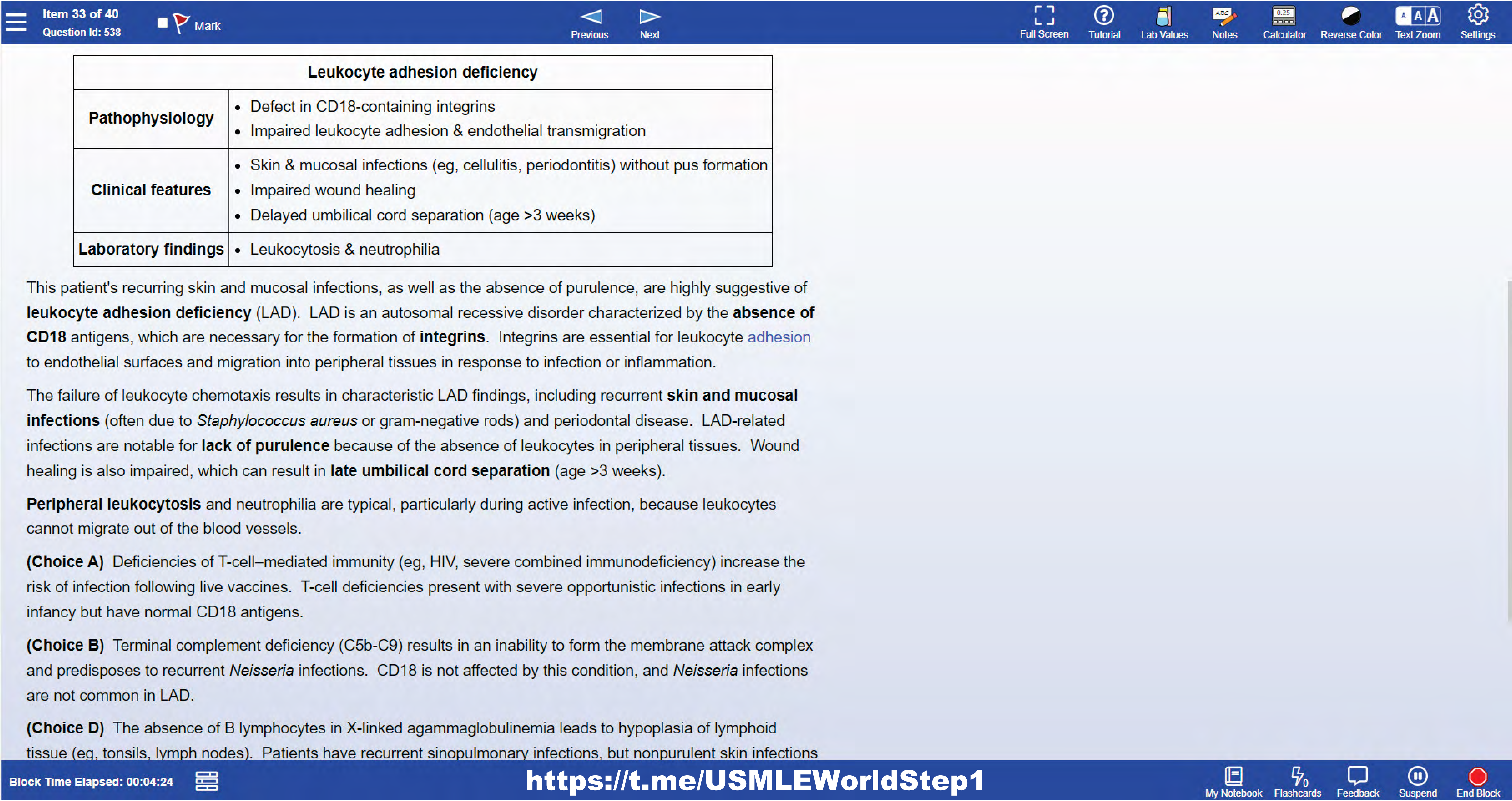

Leukocyte adhesion deficiency	
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Clinical features	• Skin & mucosal infections (eg, cellulitis, periodontitis) without pus formation • Impaired wound healing • Delayed umbilical cord separation (age >3 weeks)
Laboratory findings	• Leukocytosis & neutrophilia

This patient's recurring skin and mucosal infections, as well as the absence of purulence, are highly suggestive of **leukocyte adhesion deficiency** (LAD). LAD is an autosomal recessive disorder characterized by the **absence of CD18** antigens, which are necessary for the formation of **integrins**. Integrins are essential for leukocyte adhesion to endothelial surfaces and migration into peripheral tissues in response to infection or inflammation.

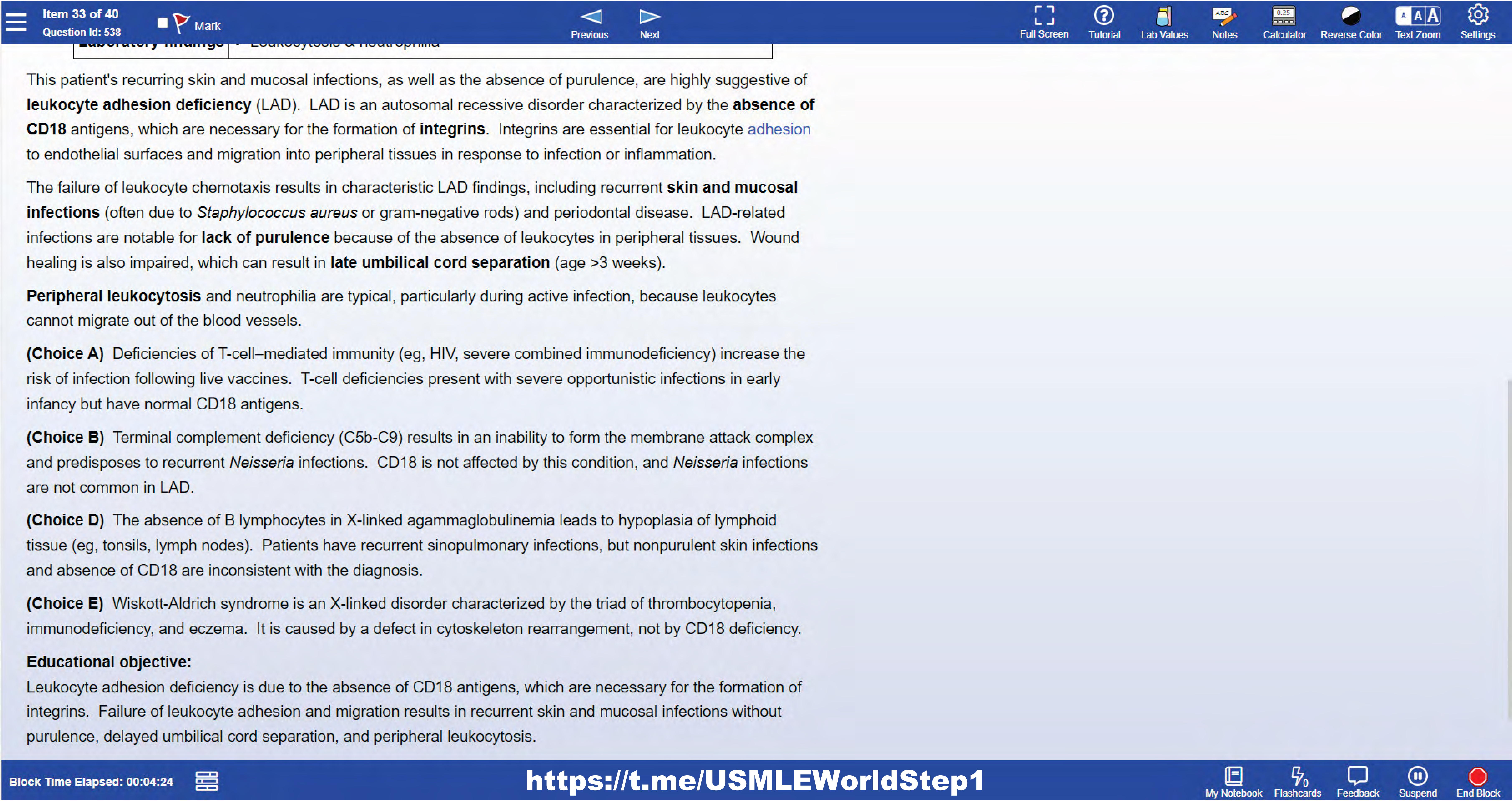
The failure of leukocyte chemotaxis results in characteristic LAD findings, including recurrent **skin and mucosal infections** (often due to *Staphylococcus aureus* or gram-negative rods) and periodontal disease. LAD-related infections are notable for **lack of purulence** because of the absence of leukocytes in peripheral tissues. Wound healing is also impaired, which can result in **late umbilical cord separation** (age >3 weeks).

Peripheral leukocytosis and neutrophilia are typical, particularly during active infection, because leukocytes cannot migrate out of the blood vessels.

(Choice A) Deficiencies of T-cell–mediated immunity (eg, HIV, severe combined immunodeficiency) increase the risk of infection following live vaccines. T-cell deficiencies present with severe opportunistic infections in early infancy but have normal CD18 antigens.

(Choice B) Terminal complement deficiency (C5b-C9) results in an inability to form the membrane attack complex and predisposes to recurrent *Neisseria* infections. CD18 is not affected by this condition, and *Neisseria* infections are not common in LAD.

(Choice D) The absence of B lymphocytes in X-linked agammaglobulinemia leads to hypoplasia of lymphoid tissue (eg, tonsils, lymph nodes). Patients have recurrent sinopulmonary infections, but nonpurulent skin infections



Laboratory findings	• Leukocytosis & neutrophilia

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(Choice B) Terminal complement deficiency (C5b-C9) results in an inability to form the membrane attack complex and predisposes to recurrent *Neisseria* infections. CD18 is not affected by this condition, and *Neisseria* infections are not common in LAD.

(Choice D) The absence of B lymphocytes in X-linked agammaglobulinemia leads to hypoplasia of lymphoid tissue (eg, tonsils, lymph nodes). Patients have recurrent sinopulmonary infections, but nonpurulent skin infections and absence of CD18 are inconsistent with the diagnosis.

(Choice E) Wiskott-Aldrich syndrome is an X-linked disorder characterized by the triad of thrombocytopenia, immunodeficiency, and eczema. It is caused by a defect in cytoskeleton rearrangement, not by CD18 deficiency.

Educational objective:
Leukocyte adhesion deficiency is due to the absence of CD18 antigens, which are necessary for the formation of integrins. Failure of leukocyte adhesion and migration results in recurrent skin and mucosal infections without purulence, delayed umbilical cord separation, and peripheral leukocytosis.

Laboratory findings • Leukocytosis & neutrophilia

This patient's recurring skin and mucosal infections, as well as the absence of purulence, are highly suggestive of

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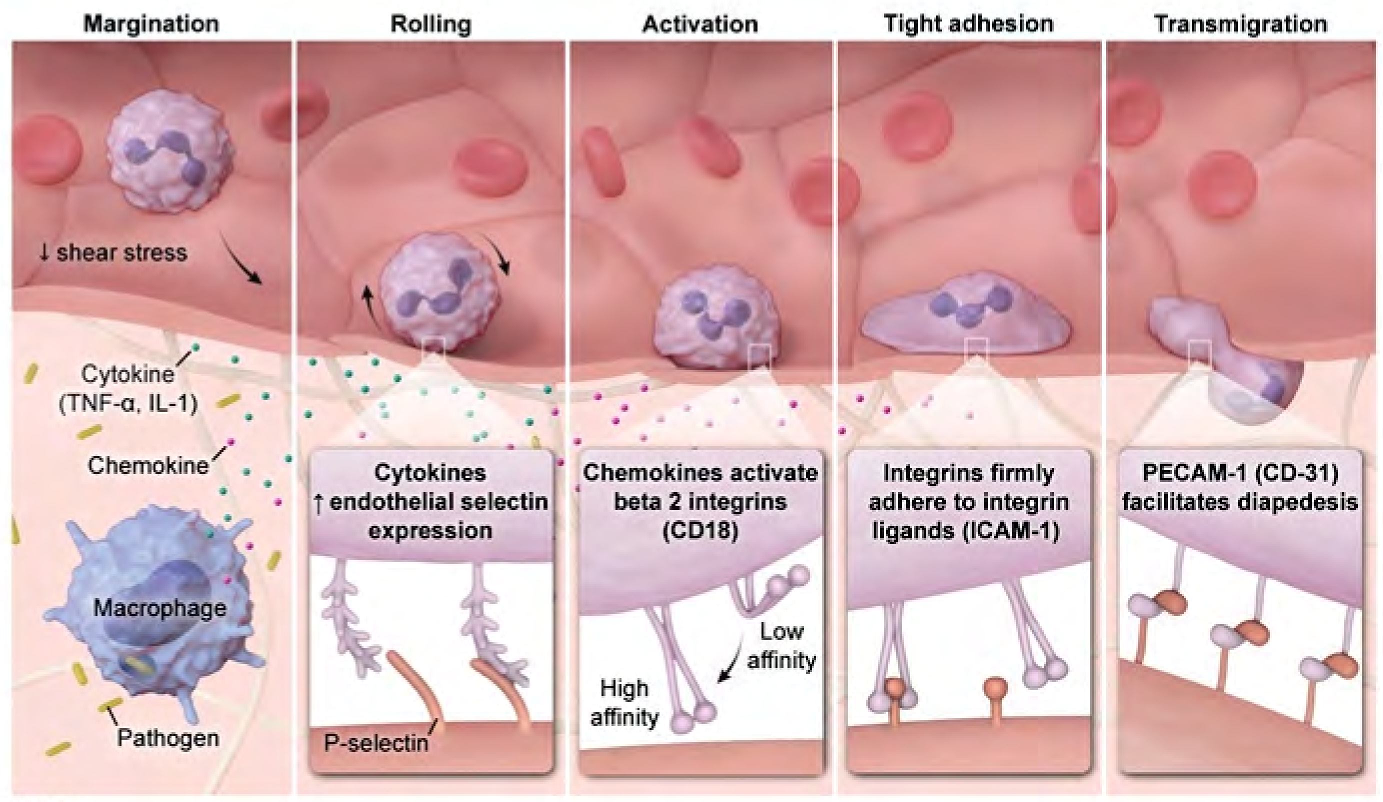
purulence, delayed umbilical cord separation, and peripheral leukocytosis.

Exhibit Display

Leukocyte adhesion cascade | Leukocyte extravasation

Leukocyte extravasation


Margination
Rolling
Activation
Tight adhesion
Transmigration
↓ shear stress
Cytokine (TNF-α, IL-1)
Chemokine
Macrophage
Pathogen
Cytokines ↑ endothelial selectin expression
P-selectin
Chemokines activate beta 2 integrins (CD18)
Low affinity
High affinity
Integrins firmly adhere to integrin ligands (ICAM-1)
PECAM-1 (CD-31) facilitates diapedesis

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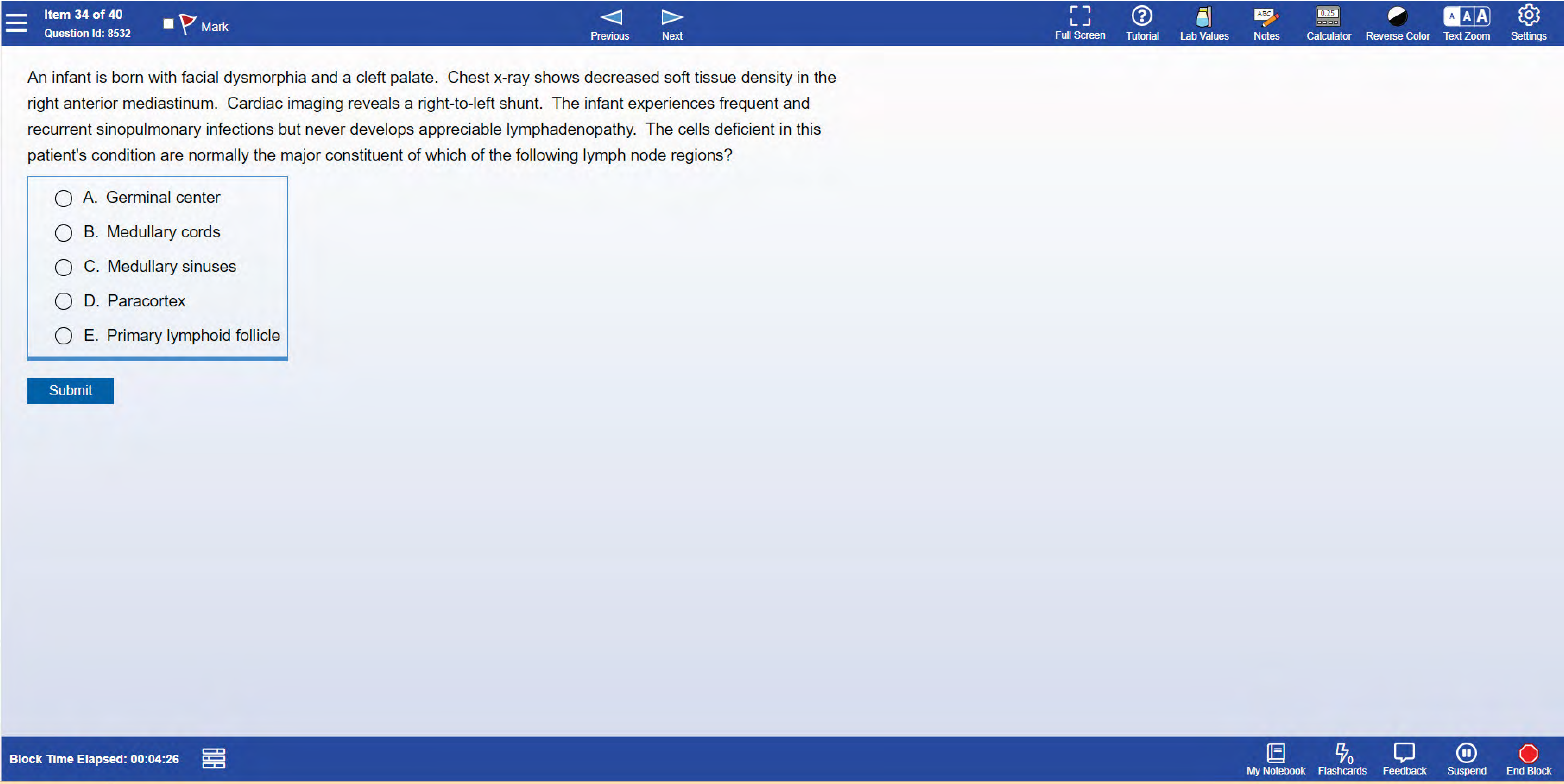
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An infant is born with facial dysmorphia and a cleft palate. Chest x-ray shows decreased soft tissue density in the right anterior mediastinum. Cardiac imaging reveals a right-to-left shunt. The infant experiences frequent and recurrent sinopulmonary infections but never develops appreciable lymphadenopathy. The cells deficient in this patient's condition are normally the major constituent of which of the following lymph node regions?

○ A. Germinal center
○ B. Medullary cords
○ C. Medullary sinuses
○ D. Paracortex
○ E. Primary lymphoid follicle

An infant is born with facial dysmorphia and a cleft palate. Chest x-ray shows decreased soft tissue density in the right anterior mediastinum. Cardiac imaging reveals a right-to-left shunt. The infant experiences frequent and recurrent sinopulmonary infections but never develops appreciable lymphadenopathy. The cells deficient in this patient's condition are normally the major constituent of which of the following lymph node regions?

- ○ A. Germinal center (23%)
- ✗ ● B. Medullary cords (3%)
- ○ C. Medullary sinuses (4%)
- ✓ ○ D. Paracortex (60%)
- ○ E. Primary lymphoid follicle (8%)

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Correct answer
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60%
Answered correctly

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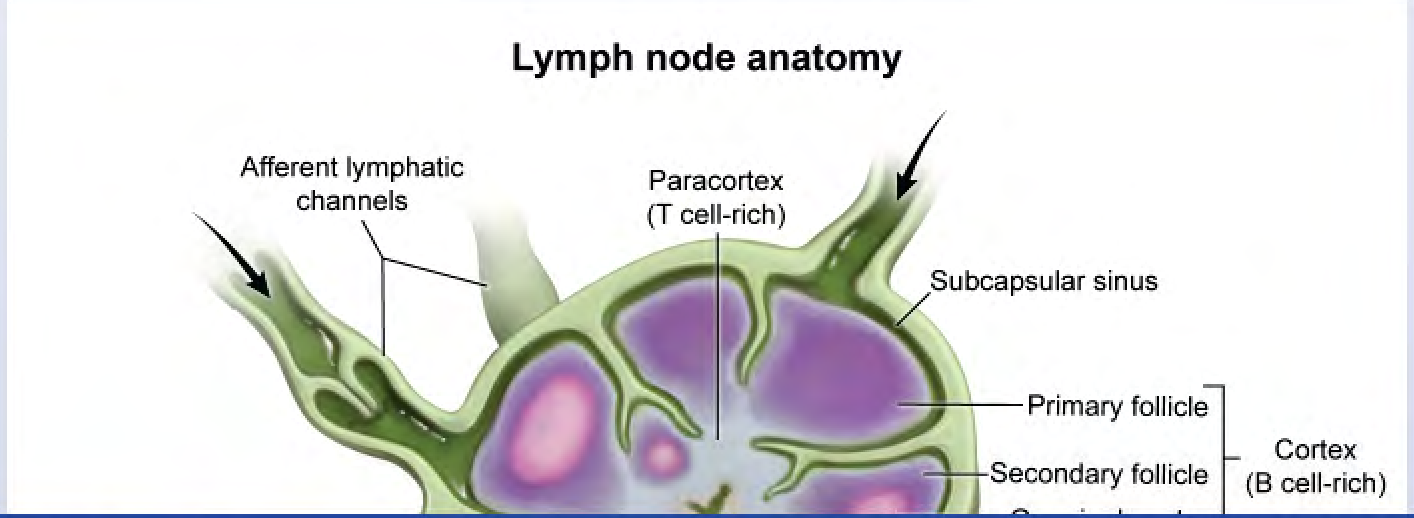
Lymph node anatomy
Afferent lymphatic channels
Paracortex (T cell-rich)
Subcapsular sinus
Primary follicle
Secondary follicle
Cortex (B cell-rich)

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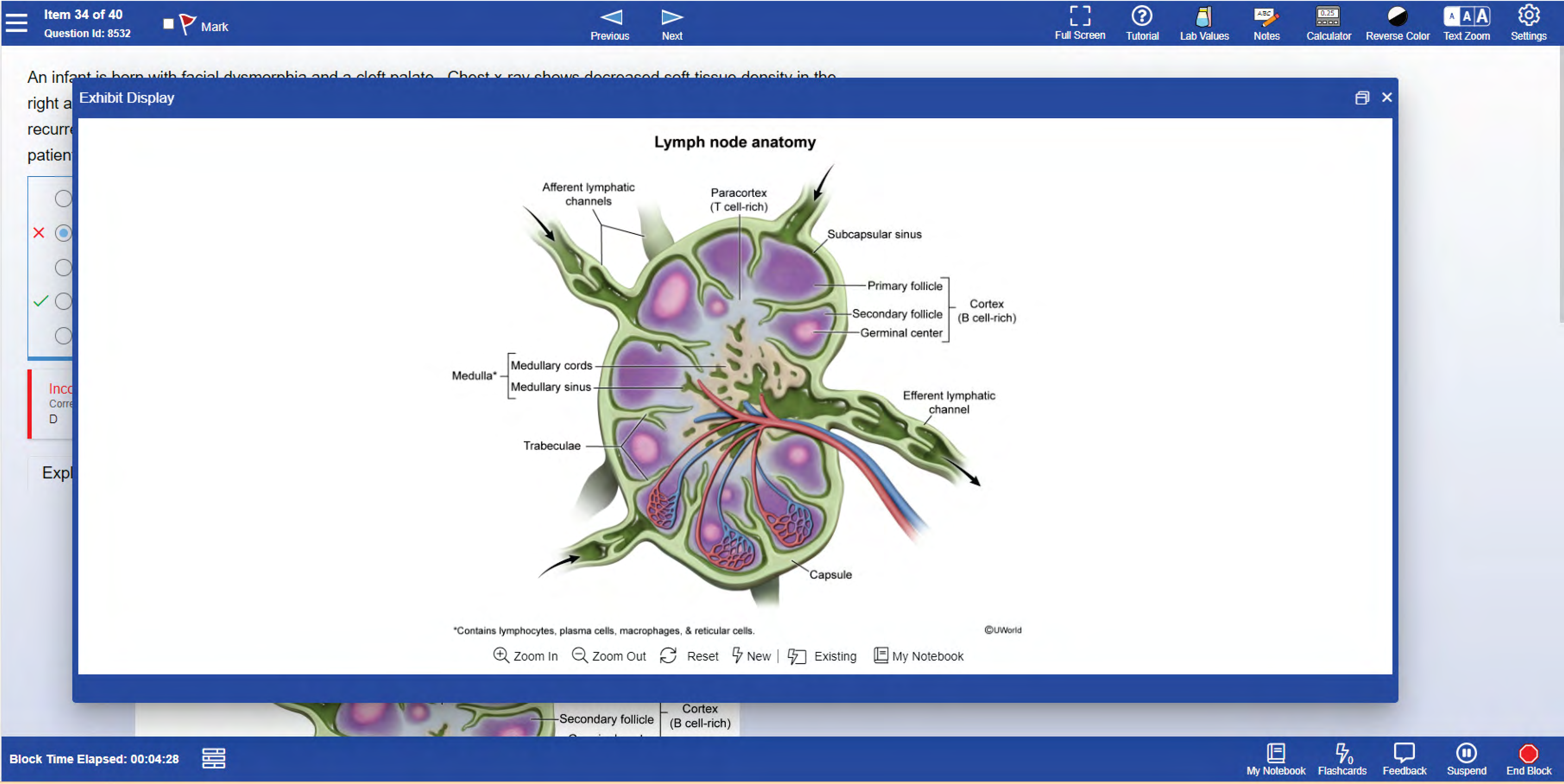
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An infant is born with facial dysmorphia and a cleft palate. Chest x-ray shows decreased soft tissue density in the

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Lymph node anatomy

Afferent lymphatic channels
Paracortex (T cell-rich)
Subcapsular sinus
Primary follicle
Secondary follicle
Germinal center
Cortex (B cell-rich)
Medulla*
Medullary cords
Medullary sinus
Efferent lymphatic channel
Trabeculae
Capsule

*Contains lymphocytes, plasma cells, macrophages, & reticular cells.

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Cortex (B cell-rich)
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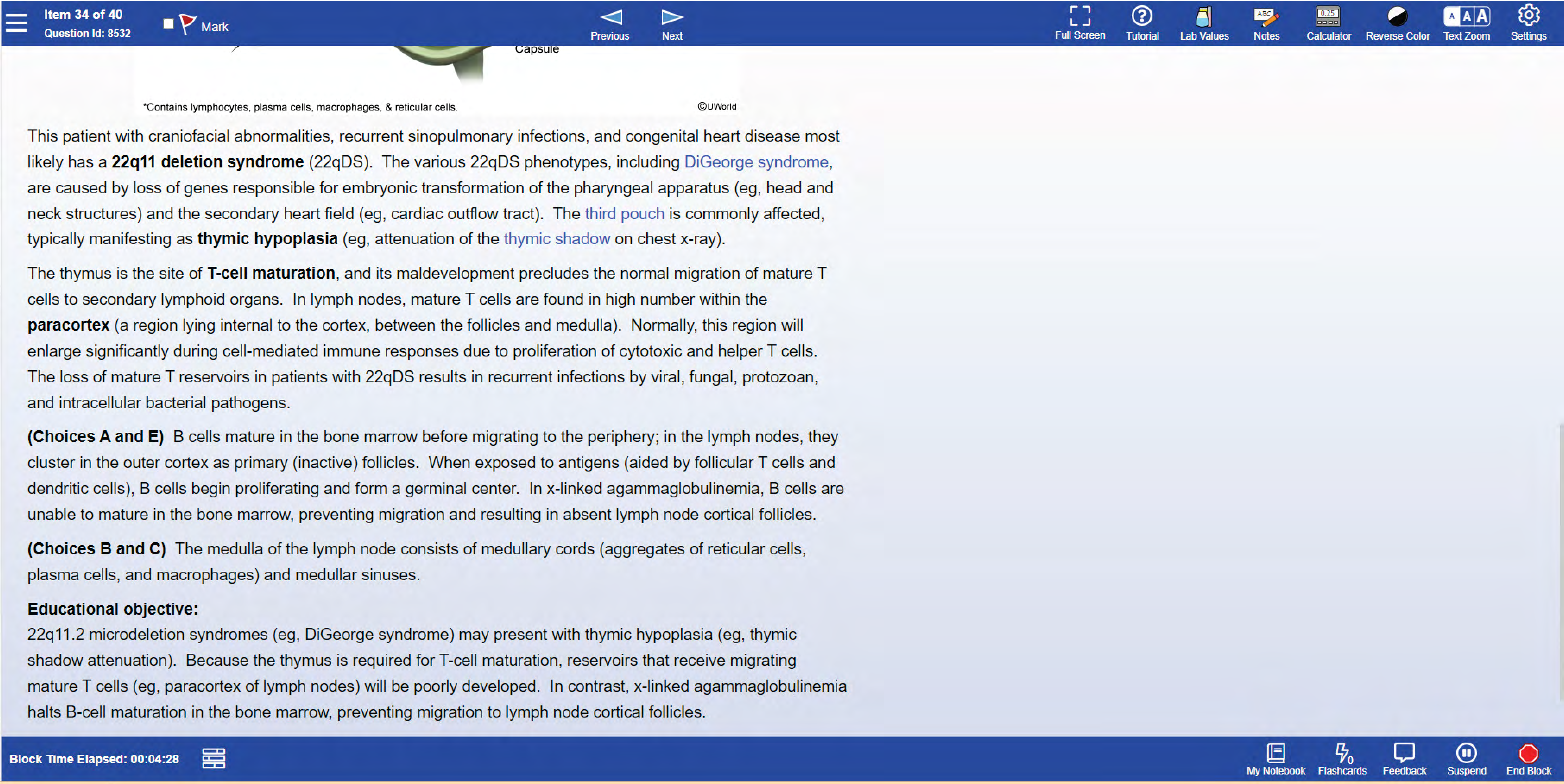

*Contains lymphocytes, plasma cells, macrophages, & reticular cells.

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This patient with craniofacial abnormalities, recurrent sinopulmonary infections, and congenital heart disease most likely has a **22q11 deletion syndrome** (22qDS). The various 22qDS phenotypes, including DiGeorge syndrome, are caused by loss of genes responsible for embryonic transformation of the pharyngeal apparatus (eg, head and neck structures) and the secondary heart field (eg, cardiac outflow tract). The third pouch is commonly affected, typically manifesting as **thymic hypoplasia** (eg, attenuation of the thymic shadow on chest x-ray).

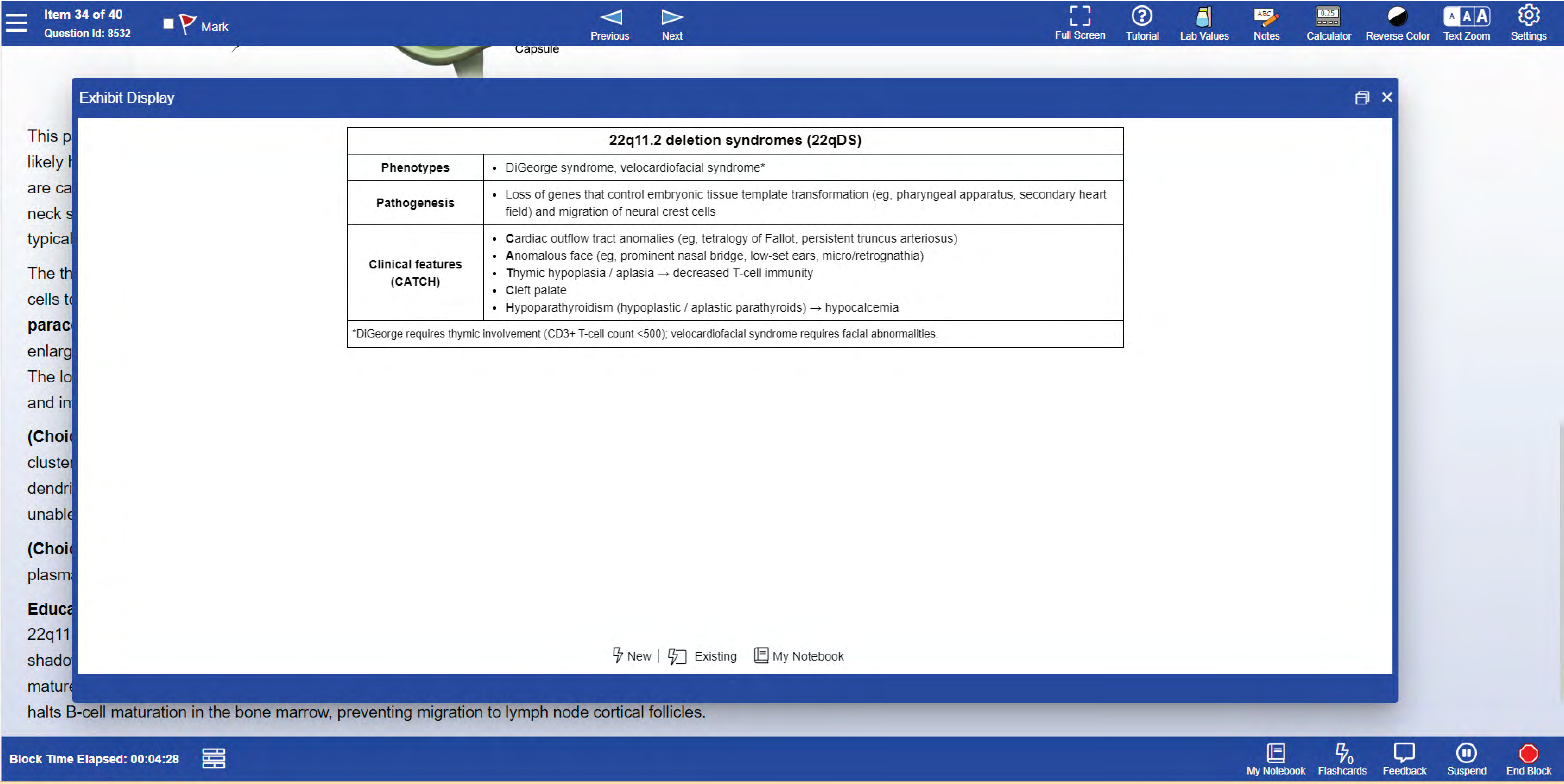
The thymus is the site of **T-cell maturation**, and its maldevelopment precludes the normal migration of mature T cells to secondary lymphoid organs. In lymph nodes, mature T cells are found in high number within the **paracortex** (a region lying internal to the cortex, between the follicles and medulla). Normally, this region will enlarge significantly during cell-mediated immune responses due to proliferation of cytotoxic and helper T cells. The loss of mature T reservoirs in patients with 22qDS results in recurrent infections by viral, fungal, protozoan, and intracellular bacterial pathogens.

(Choices A and E) B cells mature in the bone marrow before migrating to the periphery; in the lymph nodes, they cluster in the outer cortex as primary (inactive) follicles. When exposed to antigens (aided by follicular T cells and dendritic cells), B cells begin proliferating and form a germinal center. In x-linked agammaglobulinemia, B cells are unable to mature in the bone marrow, preventing migration and resulting in absent lymph node cortical follicles.

(Choices B and C) The medulla of the lymph node consists of medullary cords (aggregates of reticular cells, plasma cells, and macrophages) and medullar sinuses.

Educational objective:

22q11.2 microdeletion syndromes (eg, DiGeorge syndrome) may present with thymic hypoplasia (eg, thymic shadow attenuation). Because the thymus is required for T-cell maturation, reservoirs that receive migrating mature T cells (eg, paracortex of lymph nodes) will be poorly developed. In contrast, x-linked agammaglobulinemia halts B-cell maturation in the bone marrow, preventing migration to lymph node cortical follicles.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22q11.2 deletion syndromes (22qDS)	
Phenotypes	• DiGeorge syndrome, velocardiofacial syndrome*
Pathogenesis	• Loss of genes that control embryonic tissue template transformation (eg, pharyngeal apparatus, secondary heart field) and migration of neural crest cells
Clinical features (CATCH)	• **C**ardiac outflow tract anomalies (eg, tetralogy of Fallot, persistent truncus arteriosus) • **A**nomalous face (eg, prominent nasal bridge, low-set ears, micro/retrognathia) • **T**hymic hypoplasia / aplasia → decreased T-cell immunity • **C**left palate • **H**ypoparathyroidism (hypoplastic / aplastic parathyroids) → hypocalcemia
*DiGeorge requires thymic involvement (CD3+ T-cell count <500); velocardiofacial syndrome requires facial abnormalities.	

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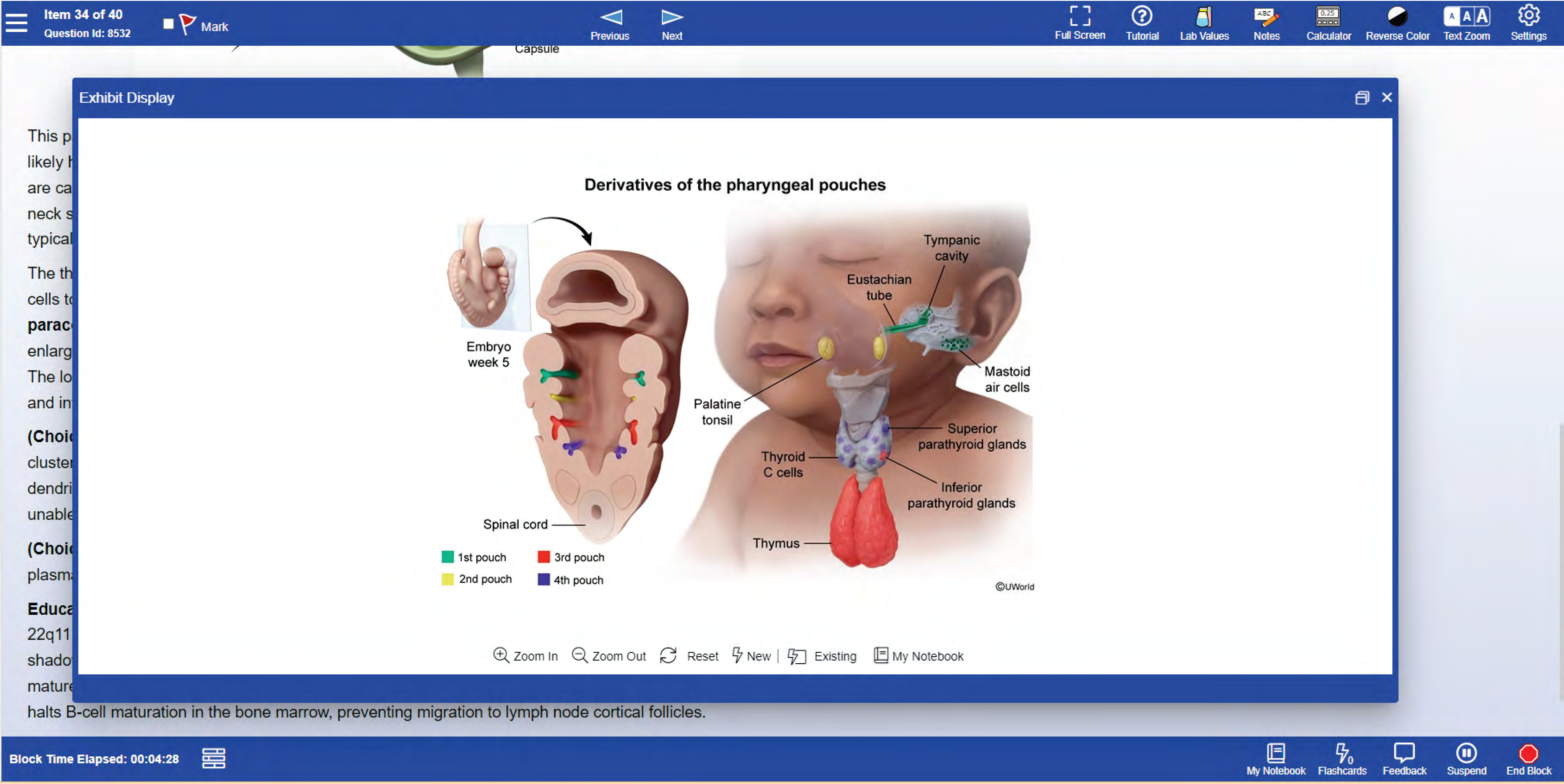

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Derivatives of the pharyngeal pouches

Embryo week 5
Spinal cord
🟩 1st pouch
🟨 2nd pouch
🟥 3rd pouch
🟦 4th pouch
Tympanic cavity
Eustachian tube
Mastoid air cells
Palatine tonsil
Superior parathyroid glands
Thyroid C cells
Inferior parathyroid glands
Thymus
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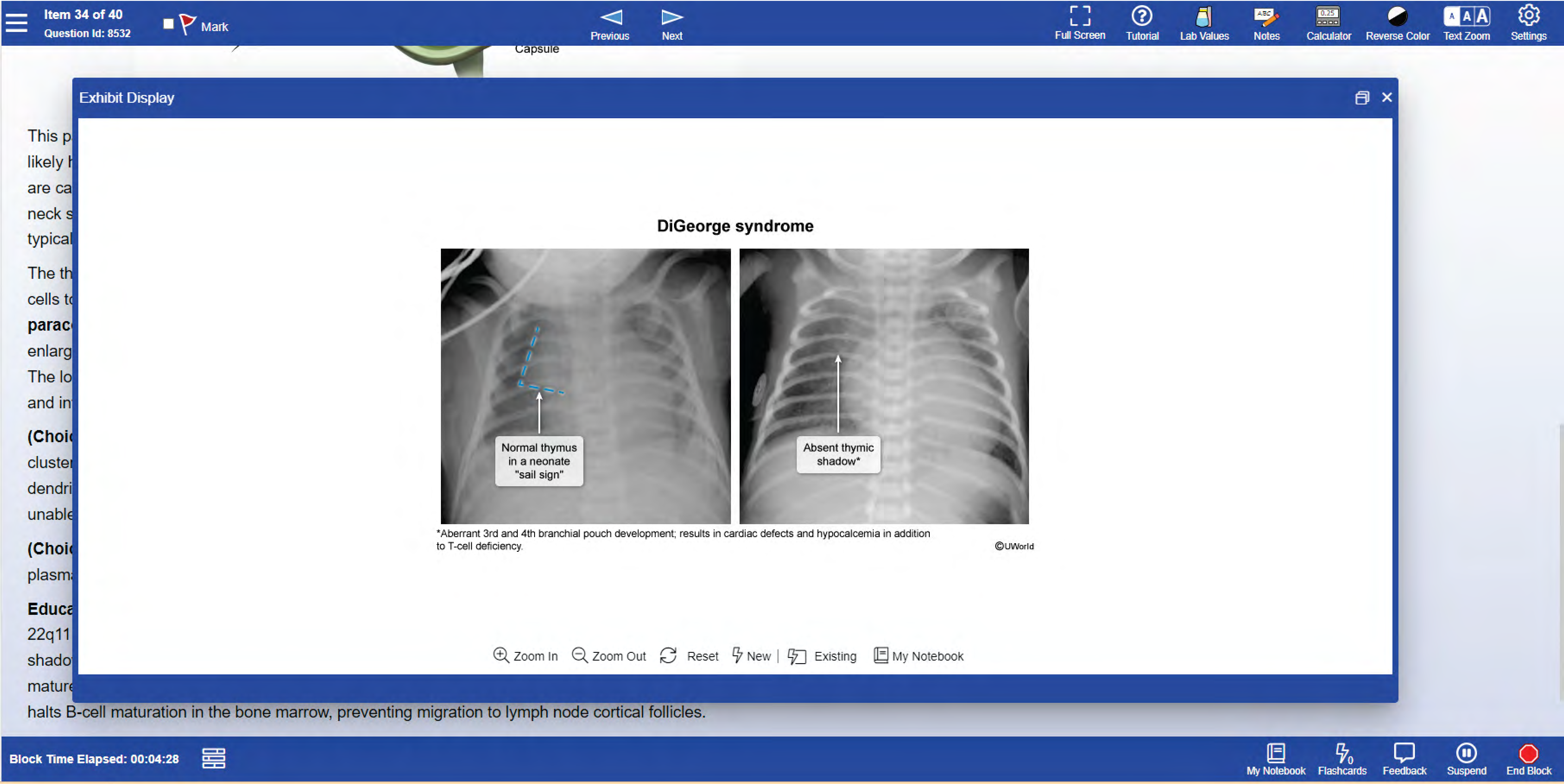
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Absent thymic shadow*
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DiGeorge syndrome

*Aberrant 3rd and 4th branchial pouch development; results in cardiac defects and hypocalcemia in addition to T-cell deficiency.

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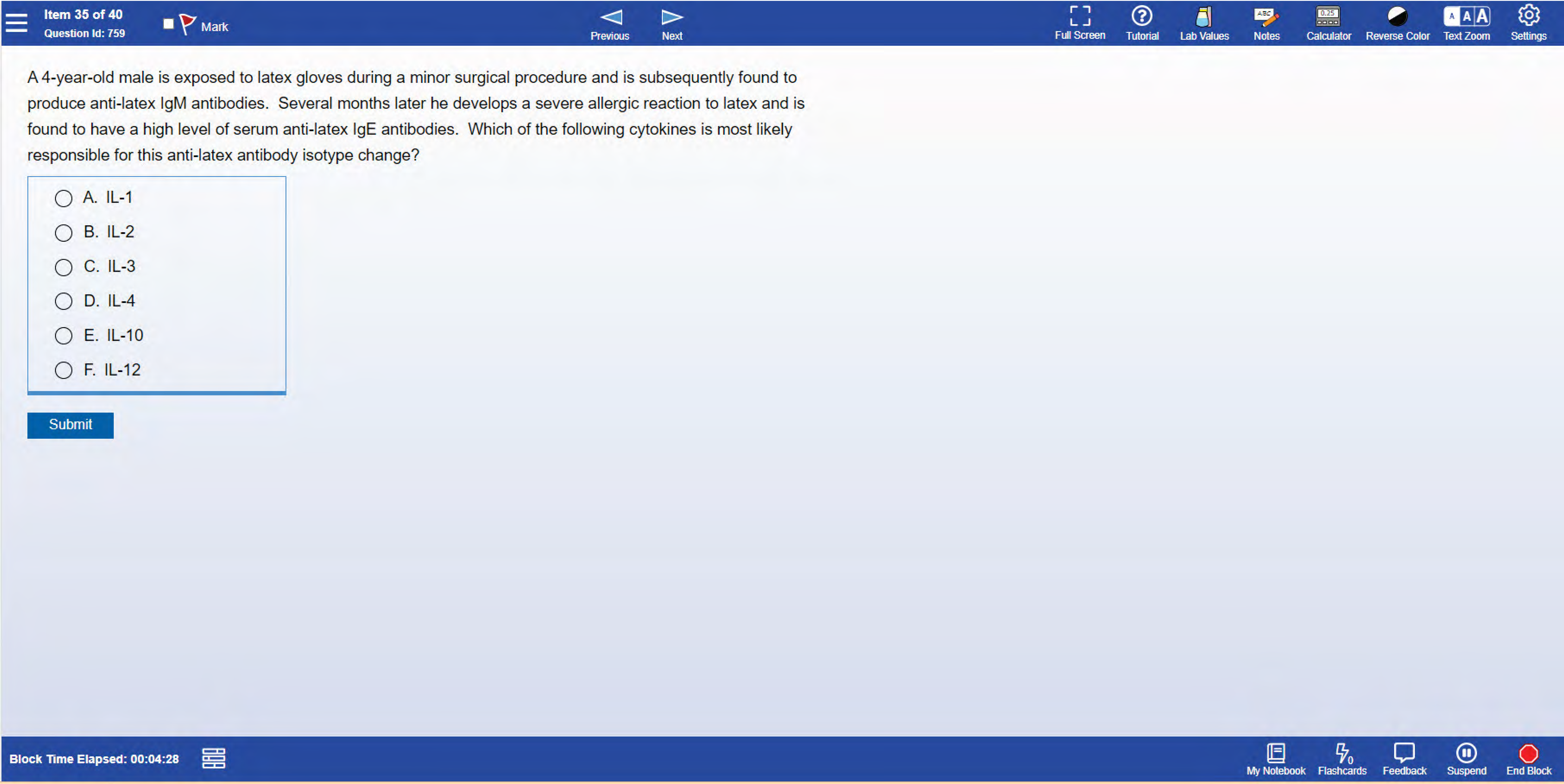
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A 4-year-old male is exposed to latex gloves during a minor surgical procedure and is subsequently found to produce anti-latex IgM antibodies. Several months later he develops a severe allergic reaction to latex and is found to have a high level of serum anti-latex IgE antibodies. Which of the following cytokines is most likely responsible for this anti-latex antibody isotype change?

○ A. IL-1
○ B. IL-2
○ C. IL-3
○ D. IL-4
○ E. IL-10
○ F. IL-12

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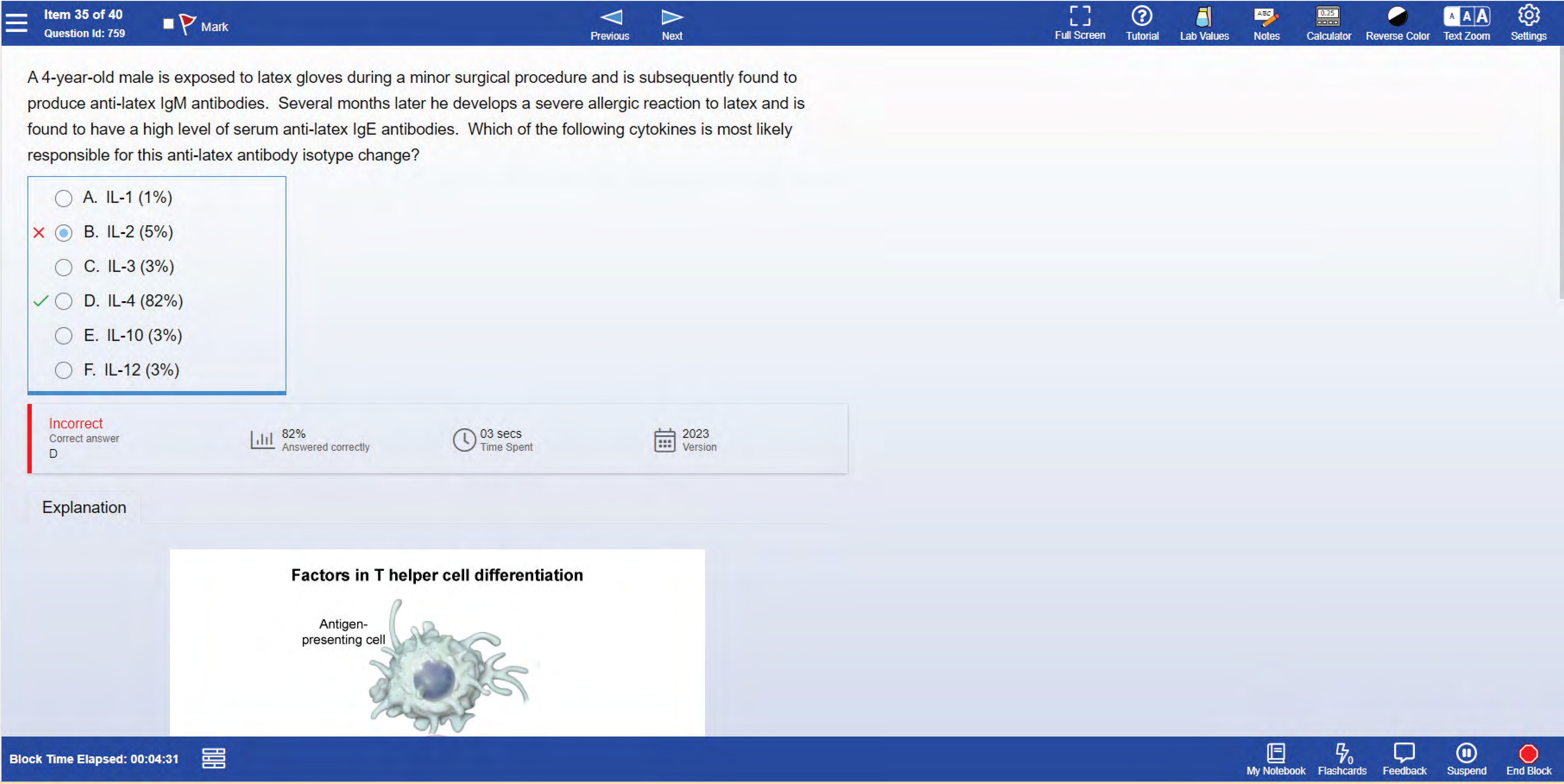
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○ A. IL-1 (1%)

✗ ● B. IL-2 (5%)

○ C. IL-3 (3%)

✓ ○ D. IL-4 (82%)

○ E. IL-10 (3%)

○ F. IL-12 (3%)

Incorrect
Correct answer
D

82%
Answered correctly

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Explanation

Factors in T helper cell differentiation

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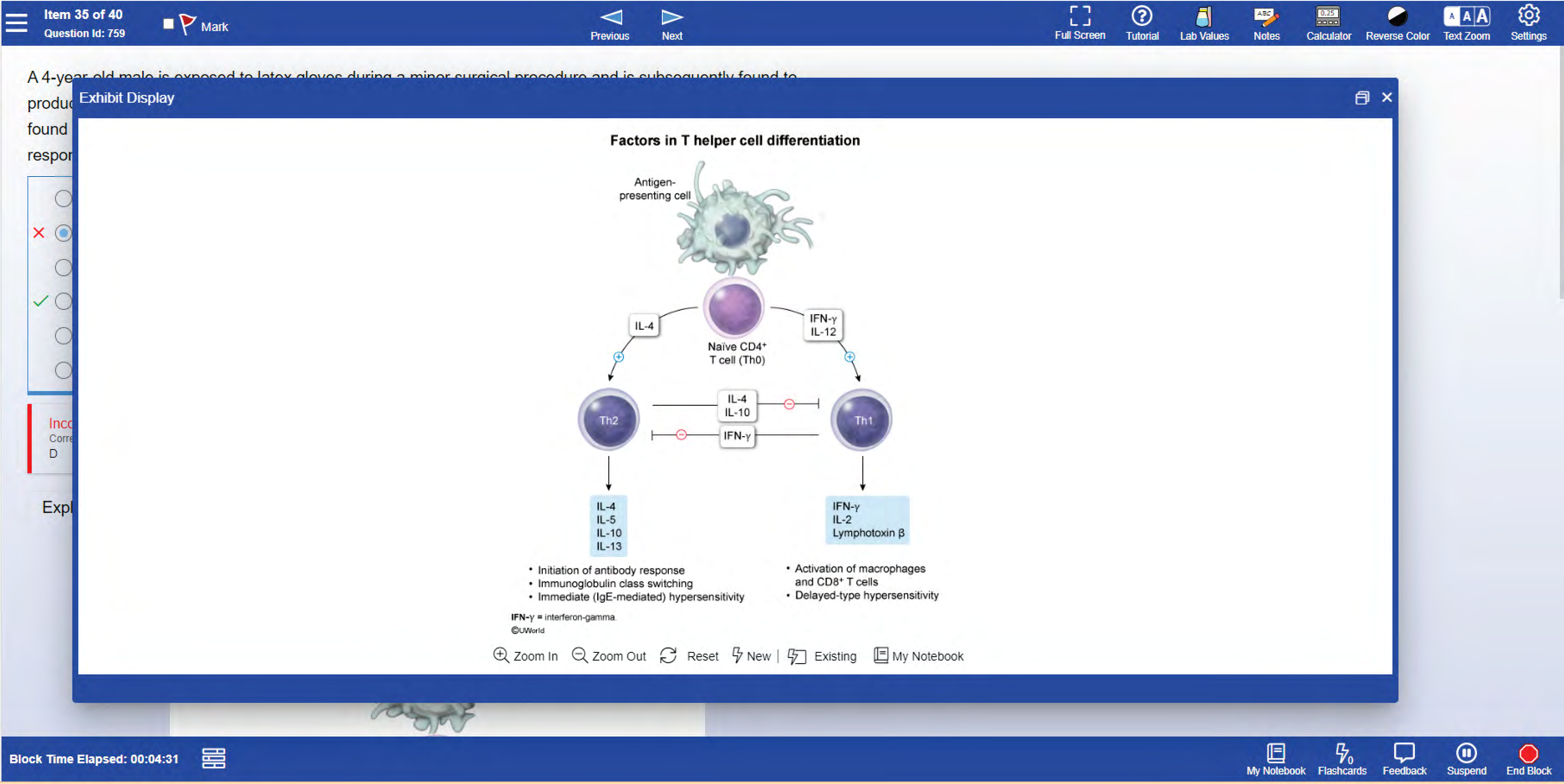
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Antigen-presenting cell
IL-4
IFN-γ
IL-12
Naïve CD4+ T cell (Th0)
Th2
Th1
IL-4
IL-10
IFN-γ
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Expl

Factors in T helper cell differentiation

IL-4
IL-5
IL-10
IL-13

- Initiation of antibody response
- Immunoglobulin class switching
- Immediate (IgE-mediated) hypersensitivity

IFN-γ
IL-2
Lymphotoxin β

- Activation of macrophages and CD8+ T cells
- Delayed-type hypersensitivity

IFN-γ = interferon-gamma

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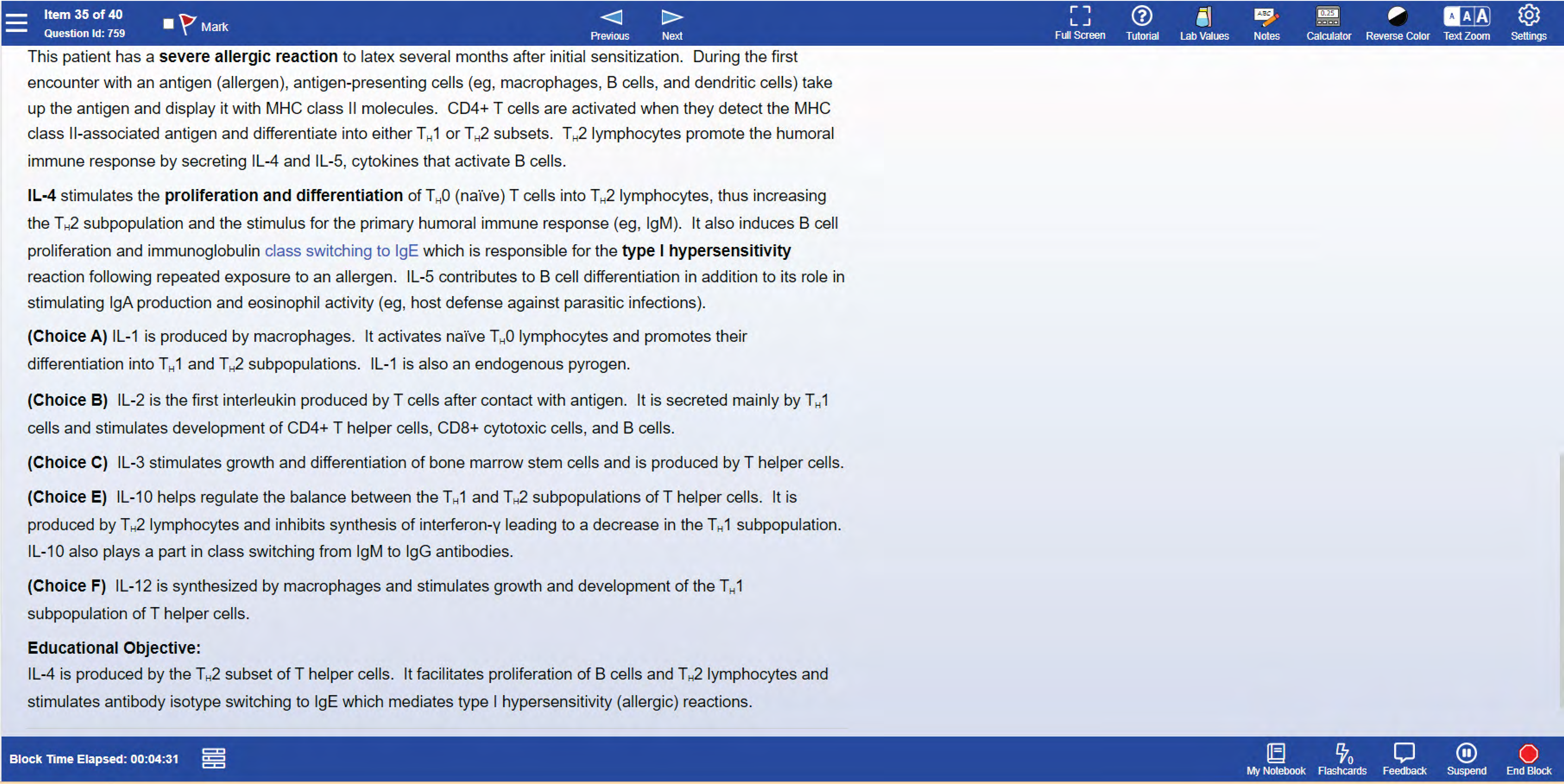


This patient has a **severe allergic reaction** to latex several months after initial sensitization. During the first encounter with an antigen (allergen), antigen-presenting cells (eg, macrophages, B cells, and dendritic cells) take up the antigen and display it with MHC class II molecules. CD4+ T cells are activated when they detect the MHC class II-associated antigen and differentiate into either T_H1 or T_H2 subsets. T_H2 lymphocytes promote the humoral immune response by secreting IL-4 and IL-5, cytokines that activate B cells.

IL-4 stimulates the **proliferation and differentiation** of T_H0 (naïve) T cells into T_H2 lymphocytes, thus increasing the T_H2 subpopulation and the stimulus for the primary humoral immune response (eg, IgM). It also induces B cell proliferation and immunoglobulin class switching to IgE which is responsible for the **type I hypersensitivity** reaction following repeated exposure to an allergen. IL-5 contributes to B cell differentiation in addition to its role in stimulating IgA production and eosinophil activity (eg, host defense against parasitic infections).

(Choice A) IL-1 is produced by macrophages. It activates naïve T_H0 lymphocytes and promotes their differentiation into T_H1 and T_H2 subpopulations. IL-1 is also an endogenous pyrogen.

(Choice B) IL-2 is the first interleukin produced by T cells after contact with antigen. It is secreted mainly by T_H1 cells and stimulates development of CD4+ T helper cells, CD8+ cytotoxic cells, and B cells.

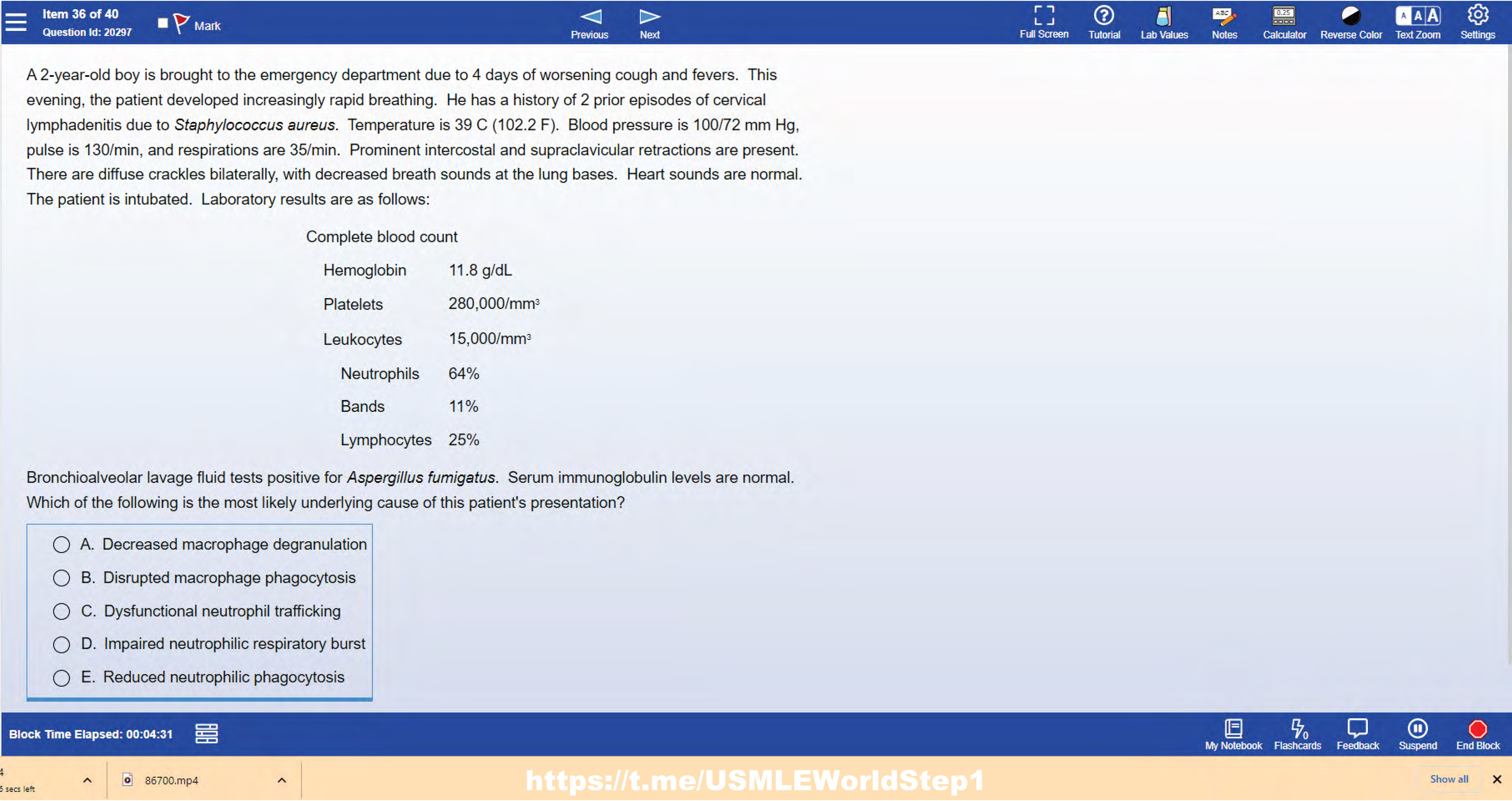
(Choice C) IL-3 stimulates growth and differentiation of bone marrow stem cells and is produced by T helper cells.

(Choice E) IL-10 helps regulate the balance between the T_H1 and T_H2 subpopulations of T helper cells. It is produced by T_H2 lymphocytes and inhibits synthesis of interferon-γ leading to a decrease in the T_H1 subpopulation. IL-10 also plays a part in class switching from IgM to IgG antibodies.

(Choice F) IL-12 is synthesized by macrophages and stimulates growth and development of the T_H1 subpopulation of T helper cells.

Educational Objective:

IL-4 is produced by the T_H2 subset of T helper cells. It facilitates proliferation of B cells and T_H2 lymphocytes and stimulates antibody isotype switching to IgE which mediates type I hypersensitivity (allergic) reactions.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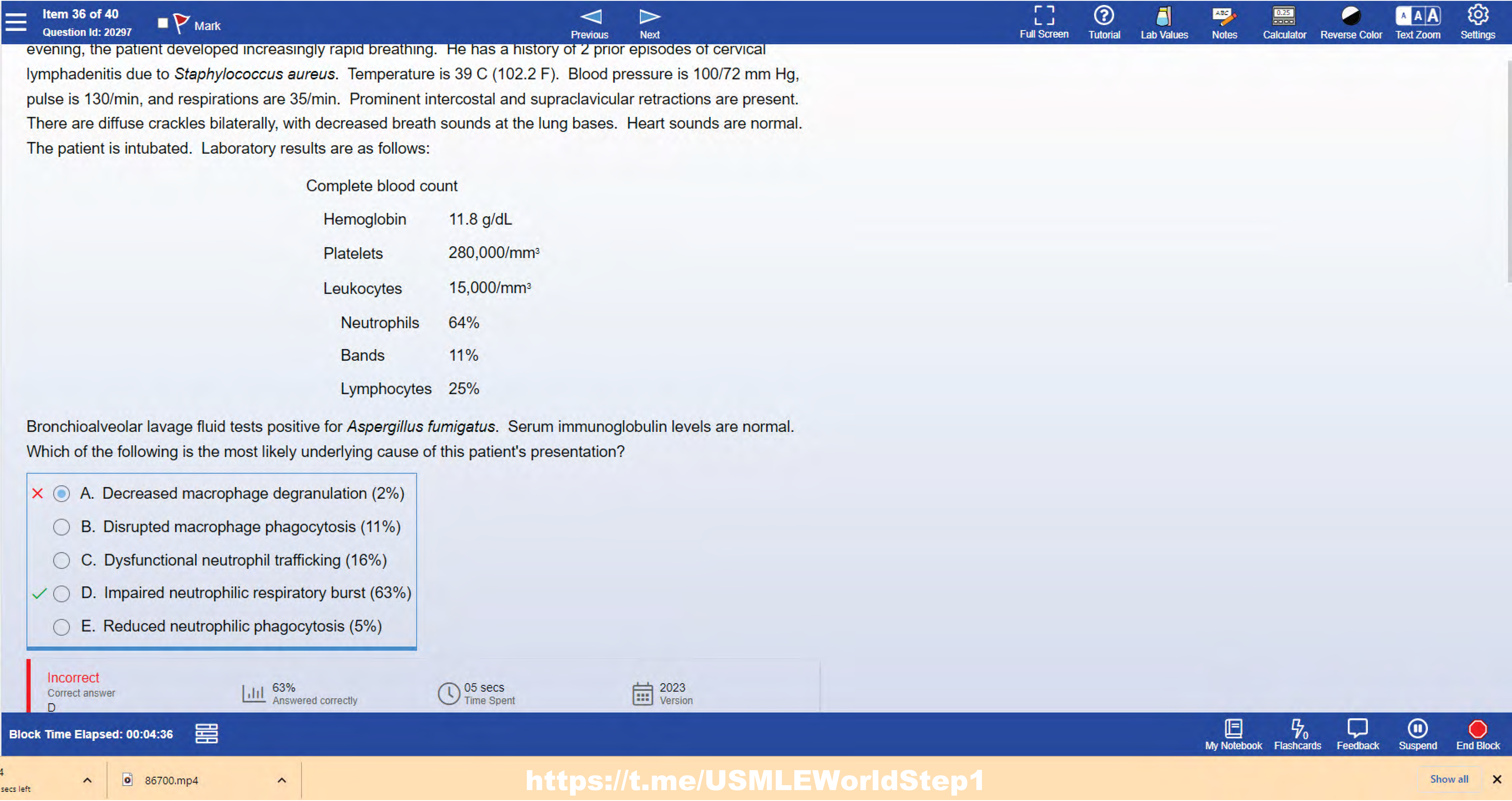
A 2-year-old boy is brought to the emergency department due to 4 days of worsening cough and fevers. This evening, the patient developed increasingly rapid breathing. He has a history of 2 prior episodes of cervical lymphadenitis due to *Staphylococcus aureus*. Temperature is 39 C (102.2 F). Blood pressure is 100/72 mm Hg, pulse is 130/min, and respirations are 35/min. Prominent intercostal and supraclavicular retractions are present. There are diffuse crackles bilaterally, with decreased breath sounds at the lung bases. Heart sounds are normal. The patient is intubated. Laboratory results are as follows:

Complete blood count	
Hemoglobin	11.8 g/dL
Platelets	280,000/mm^3
Leukocytes	15,000/mm^3
Neutrophils	64%
Bands	11%
Lymphocytes	25%

Bronchioalveolar lavage fluid tests positive for *Aspergillus fumigatus*. Serum immunoglobulin levels are normal. Which of the following is the most likely underlying cause of this patient's presentation?

○ A. Decreased macrophage degranulation
○ B. Disrupted macrophage phagocytosis
○ C. Dysfunctional neutrophil trafficking
○ D. Impaired neutrophilic respiratory burst
○ E. Reduced neutrophilic phagocytosis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evening, the patient developed increasingly rapid breathing. He has a history of 2 prior episodes of cervical lymphadenitis due to *Staphylococcus aureus*. Temperature is 39 C (102.2 F). Blood pressure is 100/72 mm Hg, pulse is 130/min, and respirations are 35/min. Prominent intercostal and supraclavicular retractions are present. There are diffuse crackles bilaterally, with decreased breath sounds at the lung bases. Heart sounds are normal. The patient is intubated. Laboratory results are as follows:

Complete blood count	
Hemoglobin	11.8 g/dL
Platelets	280,000/mm^3
Leukocytes	15,000/mm^3
Neutrophils	64%
Bands	11%
Lymphocytes	25%

Bronchioalveolar lavage fluid tests positive for *Aspergillus fumigatus*. Serum immunoglobulin levels are normal. Which of the following is the most likely underlying cause of this patient's presentation?

- ✗ ● A. Decreased macrophage degranulation (2%)
- ○ B. Disrupted macrophage phagocytosis (11%)
- ○ C. Dysfunctional neutrophil trafficking (16%)
- ✓ ○ D. Impaired neutrophilic respiratory burst (63%)
- ○ E. Reduced neutrophilic phagocytosis (5%)

Incorrect
Correct answer
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63%
Answered correctly

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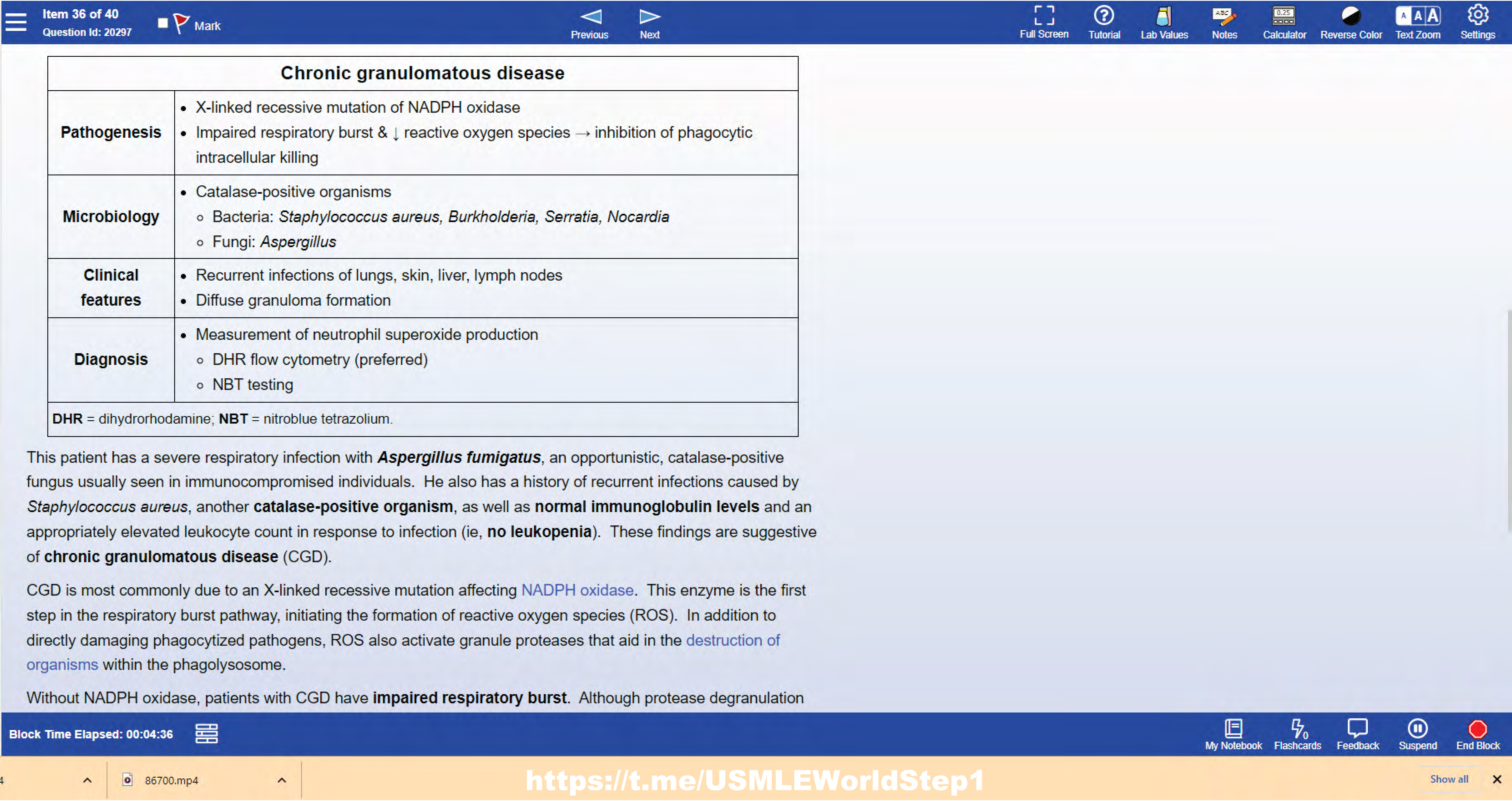
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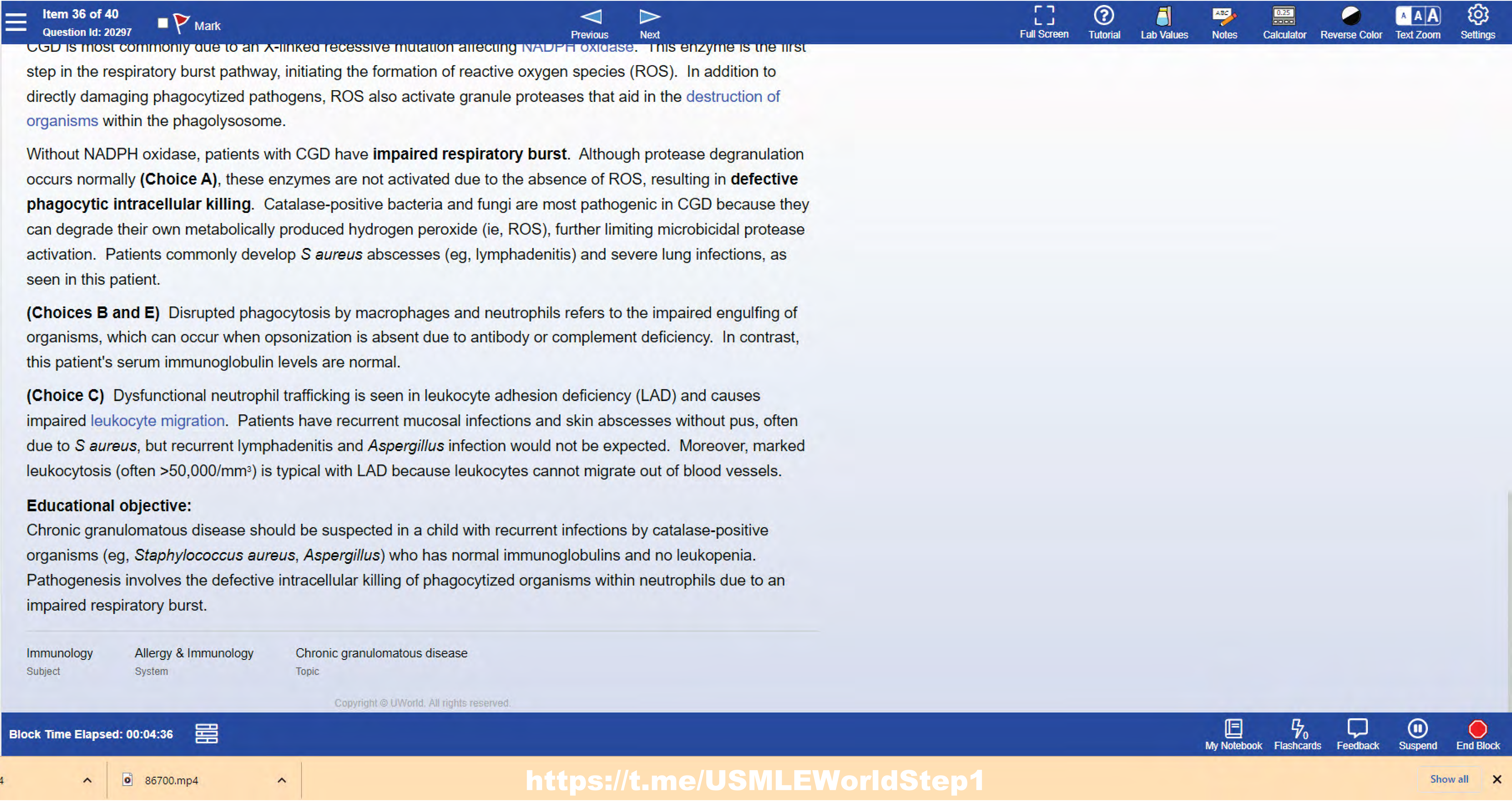
Chronic granulomatous disease	
Pathogenesis	• X-linked recessive mutation of NADPH oxidase • Impaired respiratory burst & ↓ reactive oxygen species → inhibition of phagocytic intracellular killing
Microbiology	• Catalase-positive organisms ∘ Bacteria: *Staphylococcus aureus, Burkholderia, Serratia, Nocardia* ∘ Fungi: *Aspergillus*
Clinical features	• Recurrent infections of lungs, skin, liver, lymph nodes • Diffuse granuloma formation
Diagnosis	• Measurement of neutrophil superoxide production ∘ DHR flow cytometry (preferred) ∘ NBT testing
DHR = dihydrorhodamine; **NBT** = nitroblue tetrazolium.	

This patient has a severe respiratory infection with ***Aspergillus fumigatus***, an opportunistic, catalase-positive fungus usually seen in immunocompromised individuals. He also has a history of recurrent infections caused by *Staphylococcus aureus*, another **catalase-positive organism**, as well as **normal immunoglobulin levels** and an appropriately elevated leukocyte count in response to infection (ie, **no leukopenia**). These findings are suggestive of **chronic granulomatous disease** (CGD).

CGD is most commonly due to an X-linked recessive mutation affecting NADPH oxidase. This enzyme is the first step in the respiratory burst pathway, initiating the formation of reactive oxygen species (ROS). In addition to directly damaging phagocytized pathogens, ROS also activate granule proteases that aid in the destruction of organisms within the phagolysosome.

Without NADPH oxidase, patients with CGD have **impaired respiratory burst**. Although protease degranulation



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Without NADPH oxidase, patients with CGD have **impaired respiratory burst**. Although protease degranulation occurs normally **(Choice A)**, these enzymes are not activated due to the absence of ROS, resulting in **defective phagocytic intracellular killing**. Catalase-positive bacteria and fungi are most pathogenic in CGD because they can degrade their own metabolically produced hydrogen peroxide (ie, ROS), further limiting microbicidal protease activation. Patients commonly develop *S aureus* abscesses (eg, lymphadenitis) and severe lung infections, as seen in this patient.

(Choices B and E) Disrupted phagocytosis by macrophages and neutrophils refers to the impaired engulfing of organisms, which can occur when opsonization is absent due to antibody or complement deficiency. In contrast, this patient's serum immunoglobulin levels are normal.

(Choice C) Dysfunctional neutrophil trafficking is seen in leukocyte adhesion deficiency (LAD) and causes impaired leukocyte migration. Patients have recurrent mucosal infections and skin abscesses without pus, often due to *S aureus*, but recurrent lymphadenitis and *Aspergillus* infection would not be expected. Moreover, marked leukocytosis (often >50,000/mm^3) is typical with LAD because leukocytes cannot migrate out of blood vessels.

Educational objective:

Chronic granulomatous disease should be suspected in a child with recurrent infections by catalase-positive organisms (eg, *Staphylococcus aureus*, *Aspergillus*) who has normal immunoglobulins and no leukopenia. Pathogenesis involves the defective intracellular killing of phagocytized organisms within neutrophils due to an impaired respiratory burst.

Immunology	Allergy & Immunology	Chronic granulomatous disease
Subject	System	Topic

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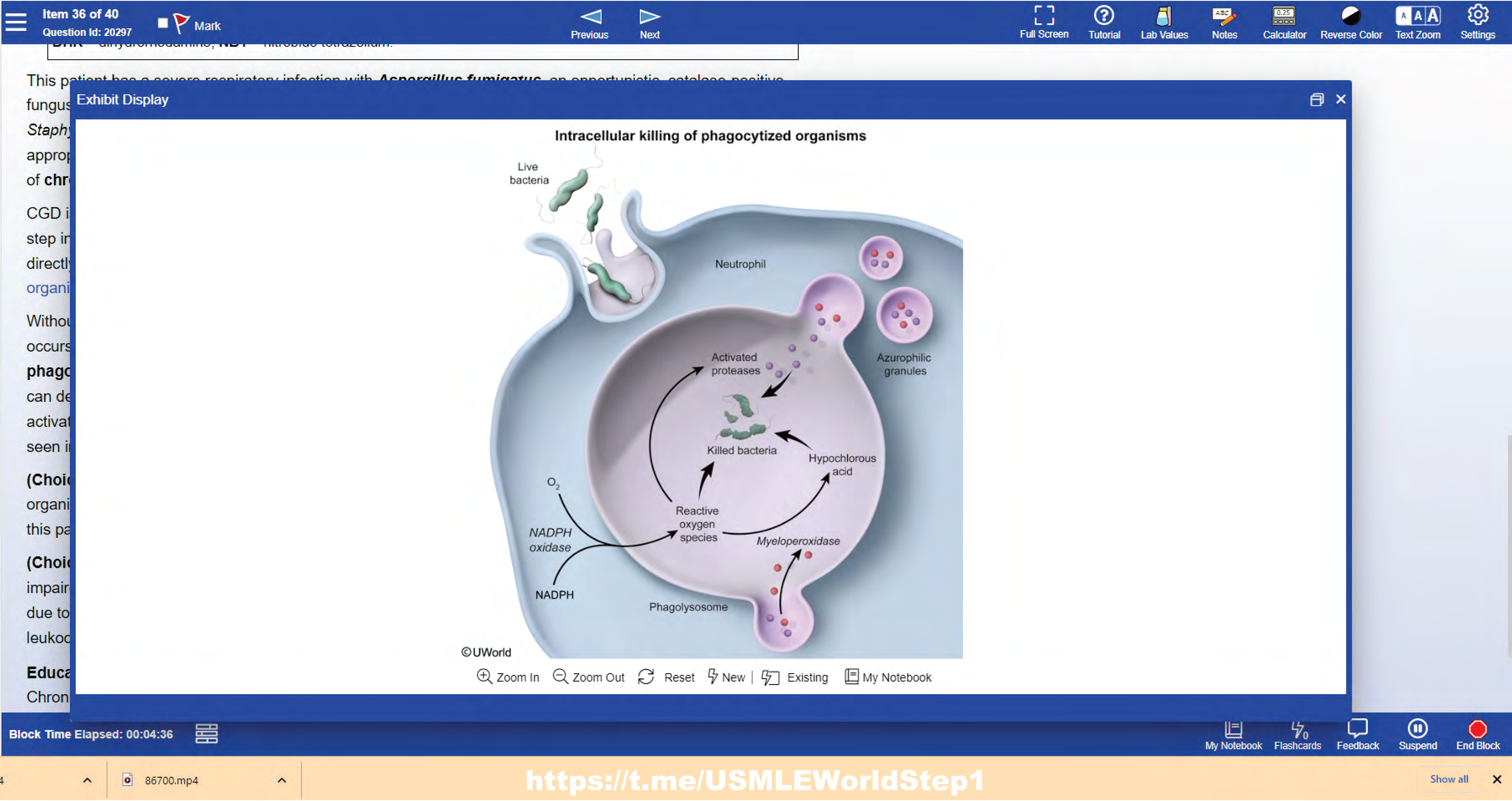
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This patient has a severe respiratory infection with ***Aspergillus fumigatus***, an opportunistic, catalase-positive

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Intracellular killing of phagocytized organisms

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Neutrophil
Azurophilic granules
Activated proteases
Killed bacteria
Hypochlorous acid
O_2
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NADPH oxidase
Myeloperoxidase
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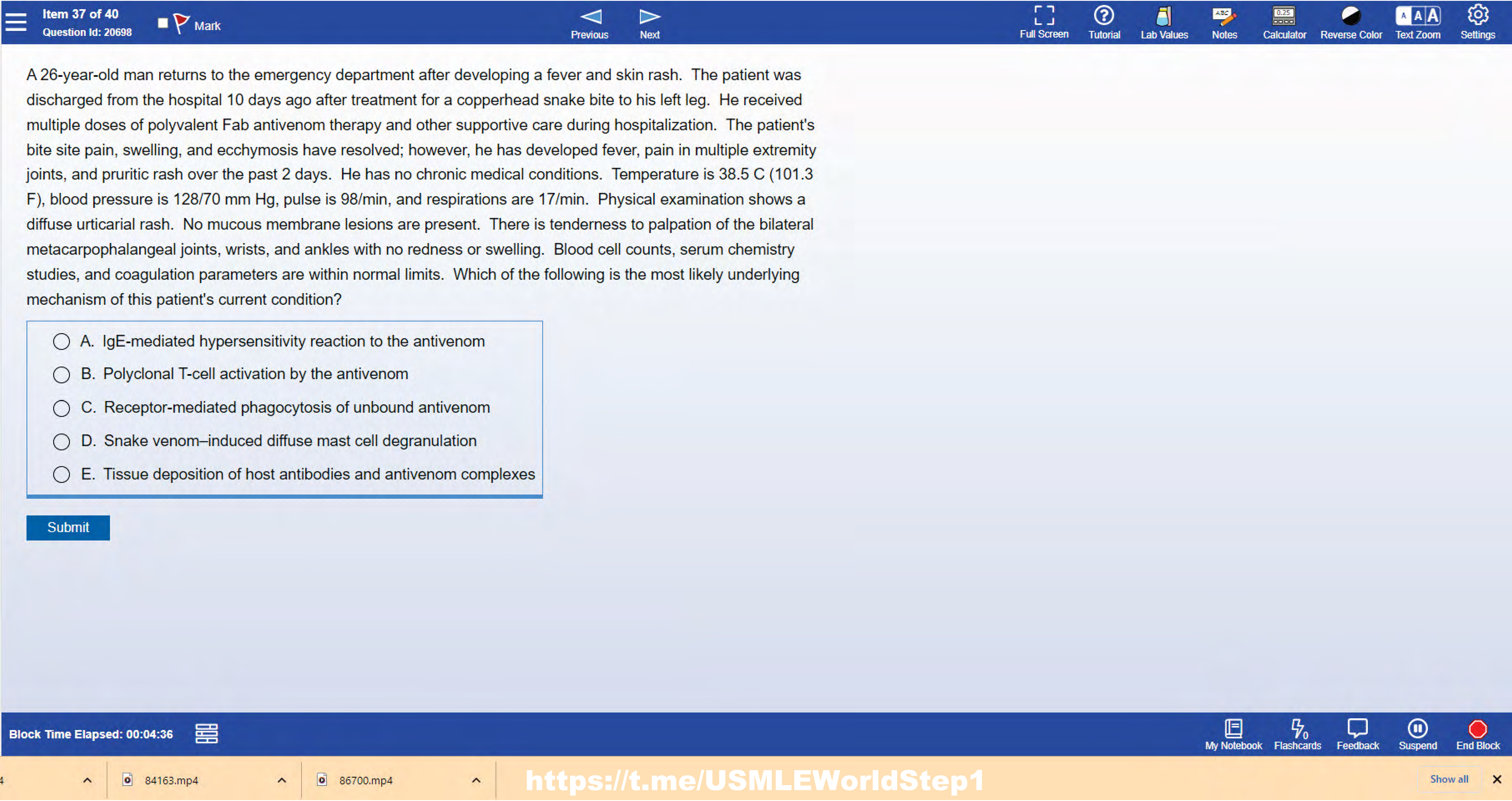
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A 26-year-old man returns to the emergency department after developing a fever and skin rash. The patient was discharged from the hospital 10 days ago after treatment for a copperhead snake bite to his left leg. He received multiple doses of polyvalent Fab antivenom therapy and other supportive care during hospitalization. The patient's bite site pain, swelling, and ecchymosis have resolved; however, he has developed fever, pain in multiple extremity joints, and pruritic rash over the past 2 days. He has no chronic medical conditions. Temperature is 38.5 C (101.3 F), blood pressure is 128/70 mm Hg, pulse is 98/min, and respirations are 17/min. Physical examination shows a diffuse urticarial rash. No mucous membrane lesions are present. There is tenderness to palpation of the bilateral metacarpophalangeal joints, wrists, and ankles with no redness or swelling. Blood cell counts, serum chemistry studies, and coagulation parameters are within normal limits. Which of the following is the most likely underlying mechanism of this patient's current condition?

- ○ A. IgE-mediated hypersensitivity reaction to the antivenom
- ○ B. Polyclonal T-cell activation by the antivenom
- ○ C. Receptor-mediated phagocytosis of unbound antivenom
- ○ D. Snake venom–induced diffuse mast cell degranulation
- ○ E. Tissue deposition of host antibodies and antivenom complexes

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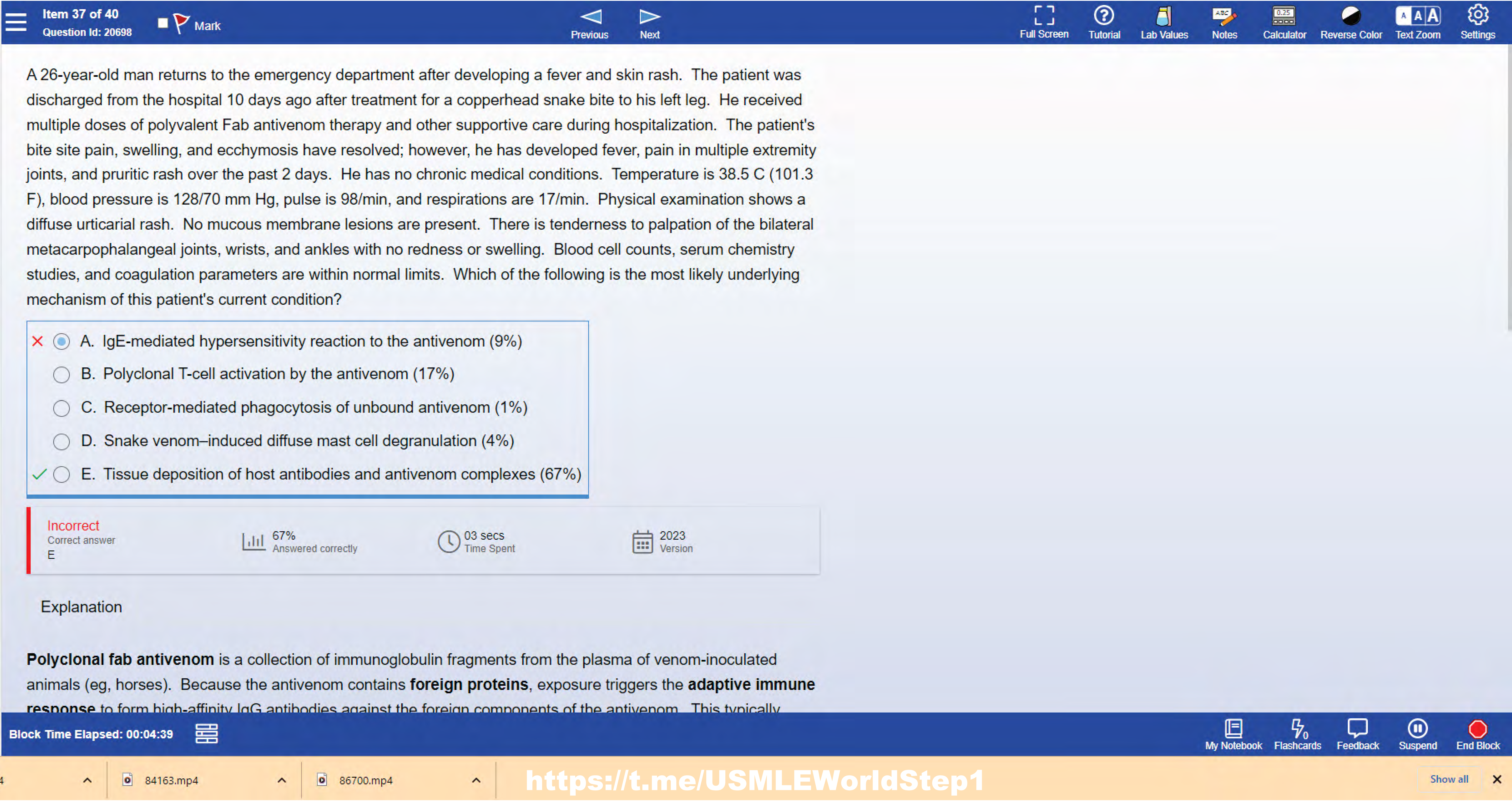
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✗ ● A. IgE-mediated hypersensitivity reaction to the antivenom (9%)
○ B. Polyclonal T-cell activation by the antivenom (17%)
○ C. Receptor-mediated phagocytosis of unbound antivenom (1%)
○ D. Snake venom–induced diffuse mast cell degranulation (4%)
✓ ○ E. Tissue deposition of host antibodies and antivenom complexes (67%)

Incorrect
Correct answer
E

67%
Answered correctly

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Explanation

Polyclonal fab antivenom is a collection of immunoglobulin fragments from the plasma of venom-inoculated animals (eg, horses). Because the antivenom contains **foreign proteins**, exposure triggers the **adaptive immune response** to form high-affinity IgG antibodies against the foreign components of the antivenom. This typically

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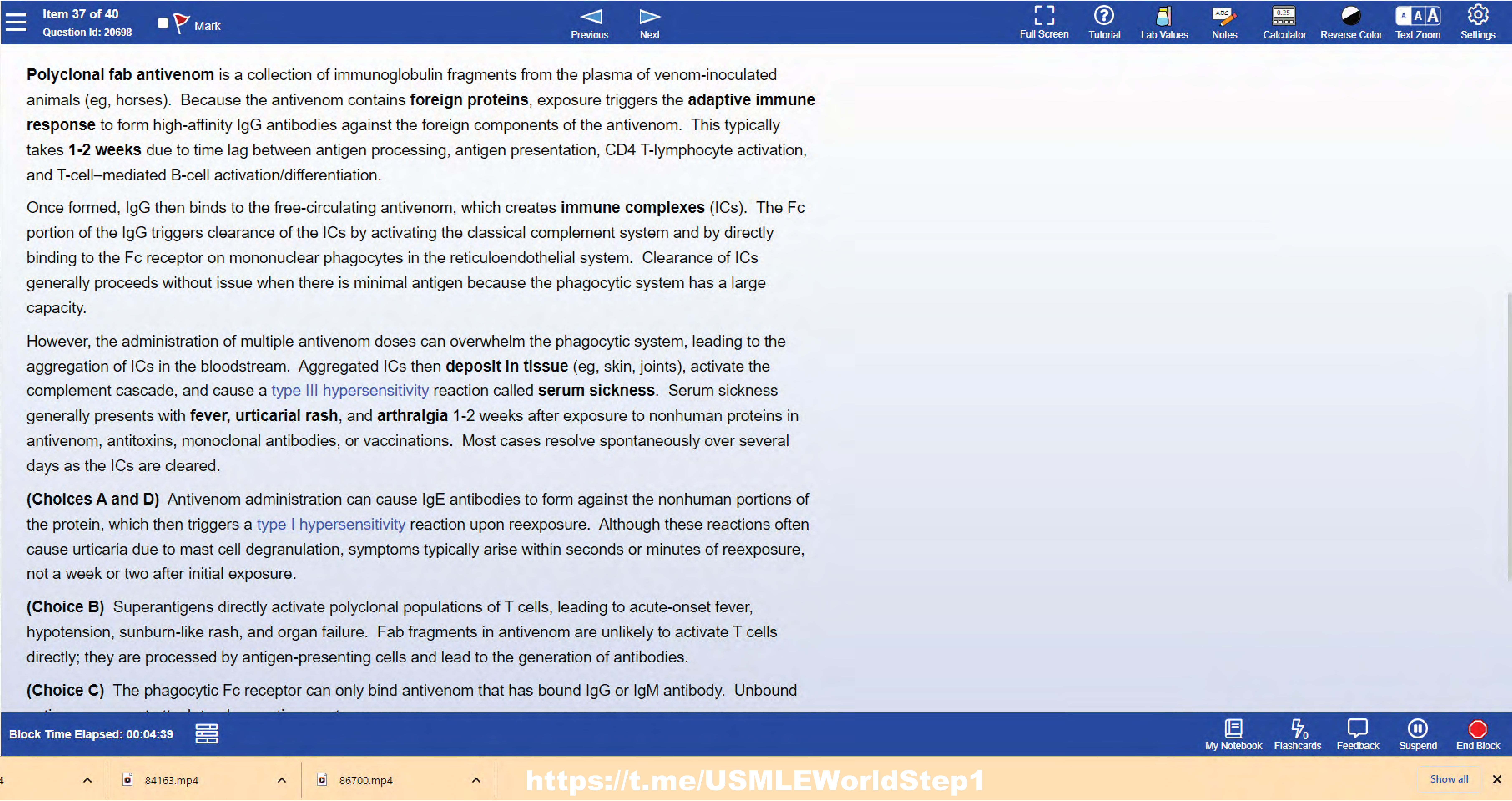


Polyclonal fab antivenom is a collection of immunoglobulin fragments from the plasma of venom-inoculated animals (eg, horses). Because the antivenom contains **foreign proteins**, exposure triggers the **adaptive immune response** to form high-affinity IgG antibodies against the foreign components of the antivenom. This typically takes **1-2 weeks** due to time lag between antigen processing, antigen presentation, CD4 T-lymphocyte activation, and T-cell–mediated B-cell activation/differentiation.

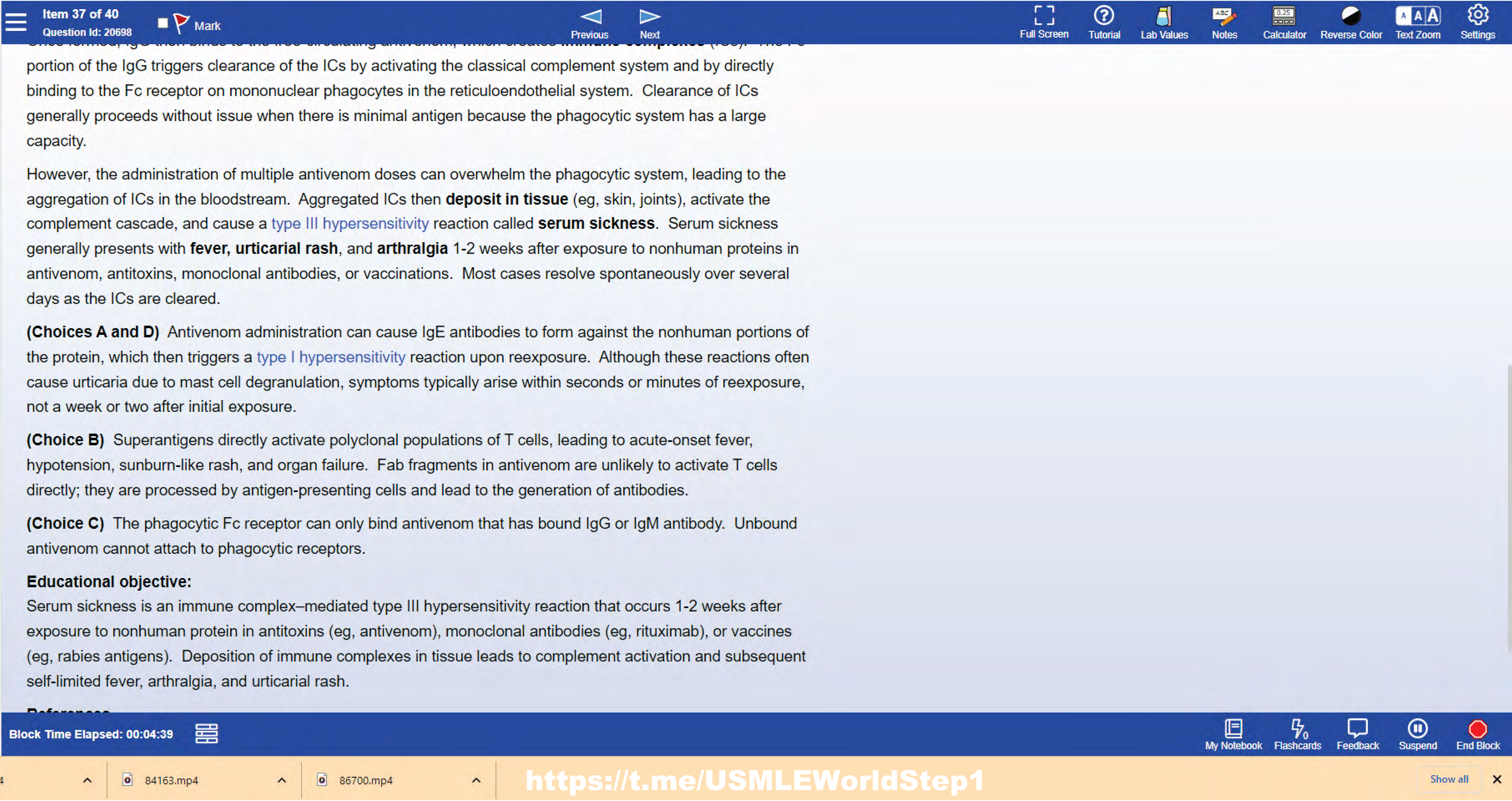
Once formed, IgG then binds to the free-circulating antivenom, which creates **immune complexes** (ICs). The Fc portion of the IgG triggers clearance of the ICs by activating the classical complement system and by directly binding to the Fc receptor on mononuclear phagocytes in the reticuloendothelial system. Clearance of ICs generally proceeds without issue when there is minimal antigen because the phagocytic system has a large capacity.

However, the administration of multiple antivenom doses can overwhelm the phagocytic system, leading to the aggregation of ICs in the bloodstream. Aggregated ICs then **deposit in tissue** (eg, skin, joints), activate the complement cascade, and cause a type III hypersensitivity reaction called **serum sickness**. Serum sickness generally presents with **fever, urticarial rash**, and **arthralgia** 1-2 weeks after exposure to nonhuman proteins in antivenom, antitoxins, monoclonal antibodies, or vaccinations. Most cases resolve spontaneously over several days as the ICs are cleared.

(Choices A and D) Antivenom administration can cause IgE antibodies to form against the nonhuman portions of the protein, which then triggers a type I hypersensitivity reaction upon reexposure. Although these reactions often cause urticaria due to mast cell degranulation, symptoms typically arise within seconds or minutes of reexposure, not a week or two after initial exposure.

(Choice B) Superantigens directly activate polyclonal populations of T cells, leading to acute-onset fever, hypotension, sunburn-like rash, and organ failure. Fab fragments in antivenom are unlikely to activate T cells directly; they are processed by antigen-presenting cells and lead to the generation of antibodies.

(Choice C) The phagocytic Fc receptor can only bind antivenom that has bound IgG or IgM antibody. Unbound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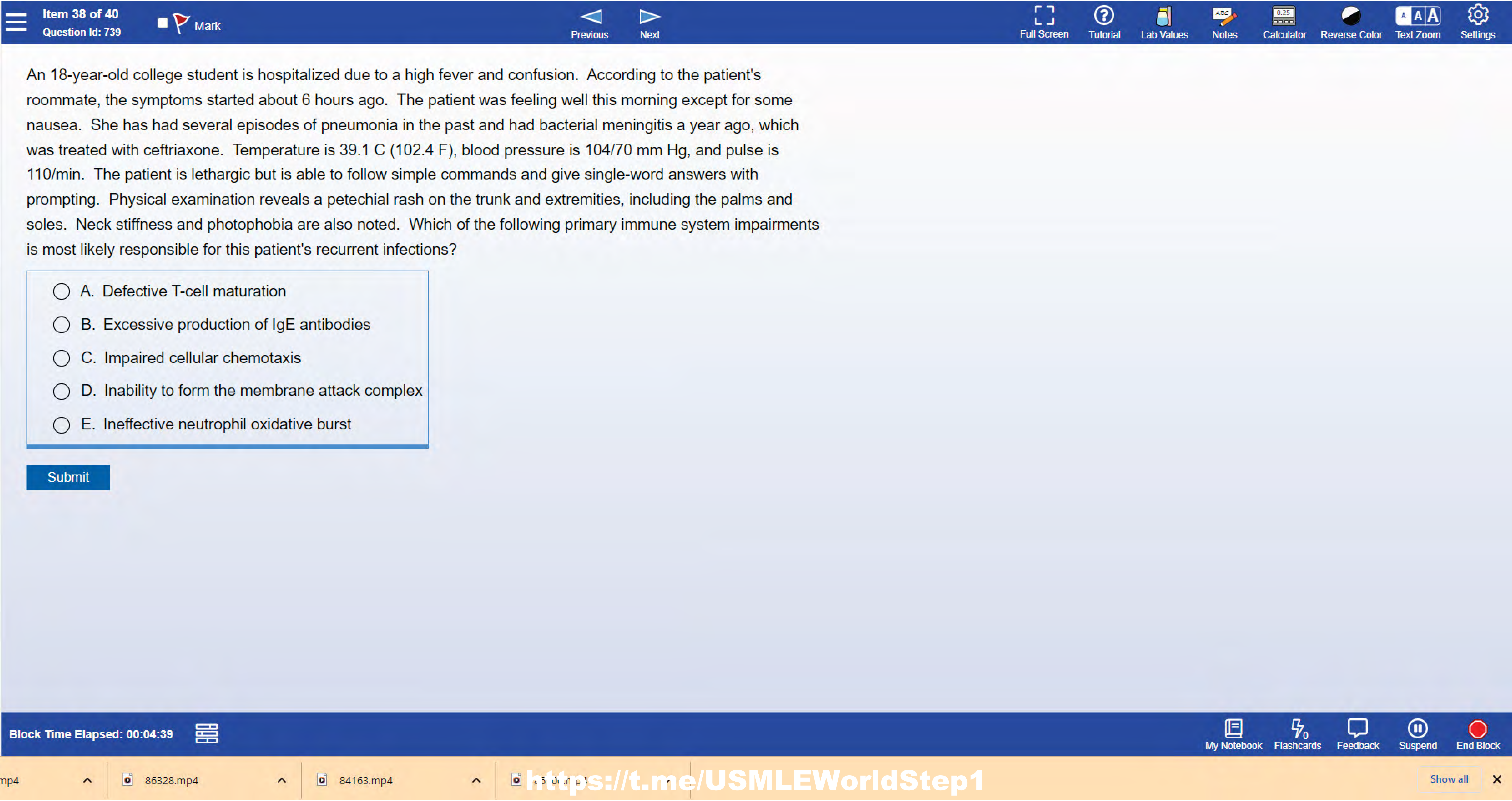
(Choice C) The phagocytic Fc receptor can only bind antivenom that has bound IgG or IgM antibody. Unbound antivenom cannot attach to phagocytic receptors.

Educational objective:

Serum sickness is an immune complex–mediated type III hypersensitivity reaction that occurs 1-2 weeks after exposure to nonhuman protein in antitoxins (eg, antivenom), monoclonal antibodies (eg, rituximab), or vaccines (eg, rabies antigens). Deposition of immune complexes in tissue leads to complement activation and subsequent self-limited fever, arthralgia, and urticarial rash.

References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An 18-year-old college student is hospitalized due to a high fever and confusion. According to the patient's roommate, the symptoms started about 6 hours ago. The patient was feeling well this morning except for some nausea. She has had several episodes of pneumonia in the past and had bacterial meningitis a year ago, which was treated with ceftriaxone. Temperature is 39.1 C (102.4 F), blood pressure is 104/70 mm Hg, and pulse is 110/min. The patient is lethargic but is able to follow simple commands and give single-word answers with prompting. Physical examination reveals a petechial rash on the trunk and extremities, including the palms and soles. Neck stiffness and photophobia are also noted. Which of the following primary immune system impairments is most likely responsible for this patient's recurrent infections?

○ A. Defective T-cell maturation
○ B. Excessive production of IgE antibodies
○ C. Impaired cellular chemotaxis
○ D. Inability to form the membrane attack complex
○ E. Ineffective neutrophil oxidative burst

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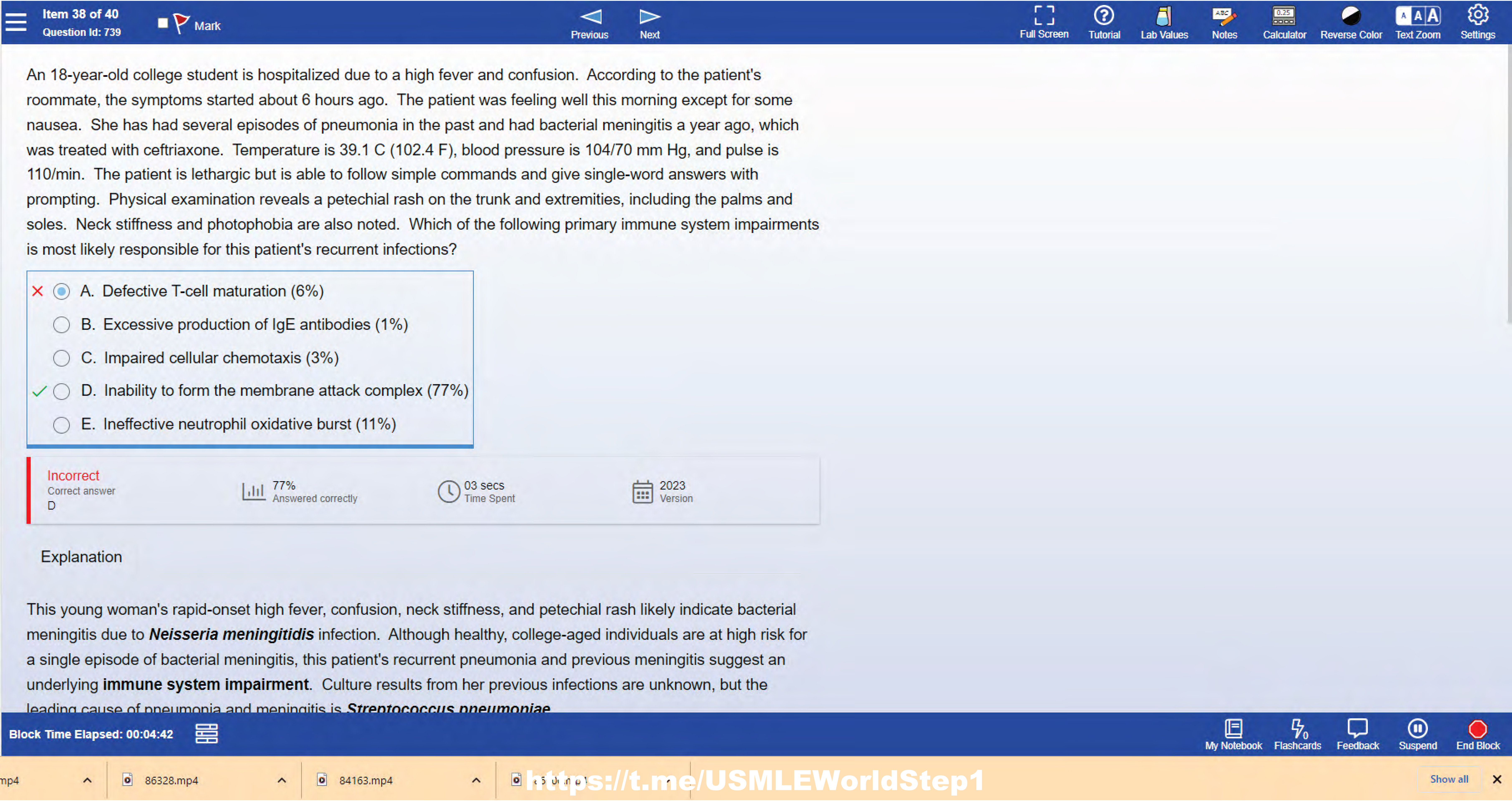
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- ✗ ● A. Defective T-cell maturation (6%)
- ○ B. Excessive production of IgE antibodies (1%)
- ○ C. Impaired cellular chemotaxis (3%)
- ✓ ○ D. Inability to form the membrane attack complex (77%)
- ○ E. Ineffective neutrophil oxidative burst (11%)

Incorrect
Correct answer
D

77%
Answered correctly

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Explanation

This young woman's rapid-onset high fever, confusion, neck stiffness, and petechial rash likely indicate bacterial meningitis due to ***Neisseria meningitidis*** infection. Although healthy, college-aged individuals are at high risk for a single episode of bacterial meningitis, this patient's recurrent pneumonia and previous meningitis suggest an underlying **immune system impairment**. Culture results from her previous infections are unknown, but the leading cause of pneumonia and meningitis is ***Streptococcus pneumoniae***

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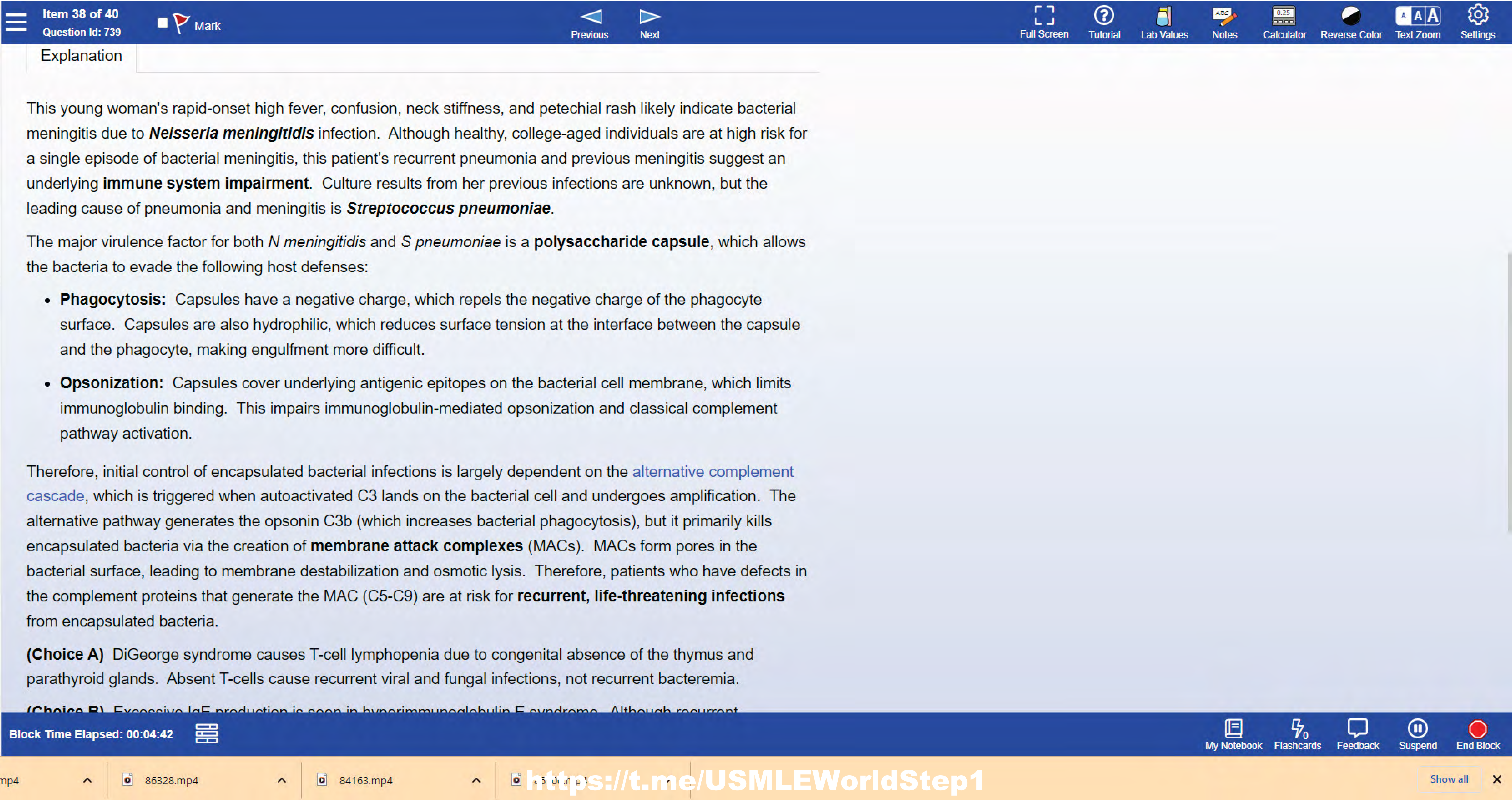
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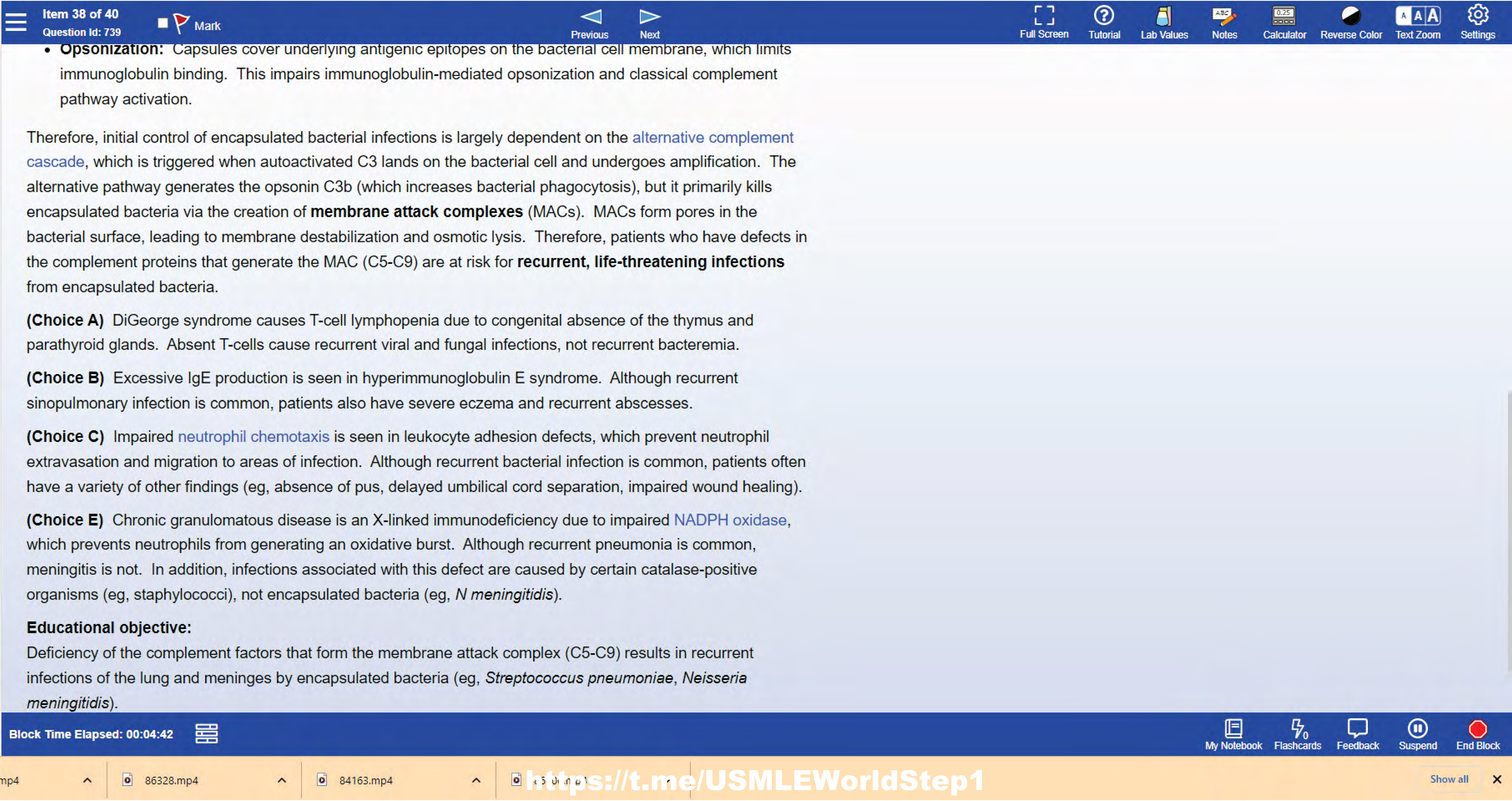
The major virulence factor for both *N meningitidis* and *S pneumoniae* is a **polysaccharide capsule**, which allows the bacteria to evade the following host defenses:

- **Phagocytosis:** Capsules have a negative charge, which repels the negative charge of the phagocyte surface. Capsules are also hydrophilic, which reduces surface tension at the interface between the capsule and the phagocyte, making engulfment more difficult.
- **Opsonization:** Capsules cover underlying antigenic epitopes on the bacterial cell membrane, which limits immunoglobulin binding. This impairs immunoglobulin-mediated opsonization and classical complement pathway activation.

Therefore, initial control of encapsulated bacterial infections is largely dependent on the alternative complement cascade, which is triggered when autoactivated C3 lands on the bacterial cell and undergoes amplification. The alternative pathway generates the opsonin C3b (which increases bacterial phagocytosis), but it primarily kills encapsulated bacteria via the creation of **membrane attack complexes** (MACs). MACs form pores in the bacterial surface, leading to membrane destabilization and osmotic lysis. Therefore, patients who have defects in the complement proteins that generate the MAC (C5-C9) are at risk for **recurrent, life-threatening infections** from encapsulated bacteria.

(Choice A) DiGeorge syndrome causes T-cell lymphopenia due to congenital absence of the thymus and parathyroid glands. Absent T-cells cause recurrent viral and fungal infections, not recurrent bacteremia.

(Choice B) Excessive IgE production is seen in hyperimmunoglobulin E syndrome. Although recurrent



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(Choice A) DiGeorge syndrome causes T-cell lymphopenia due to congenital absence of the thymus and parathyroid glands. Absent T-cells cause recurrent viral and fungal infections, not recurrent bacteremia.

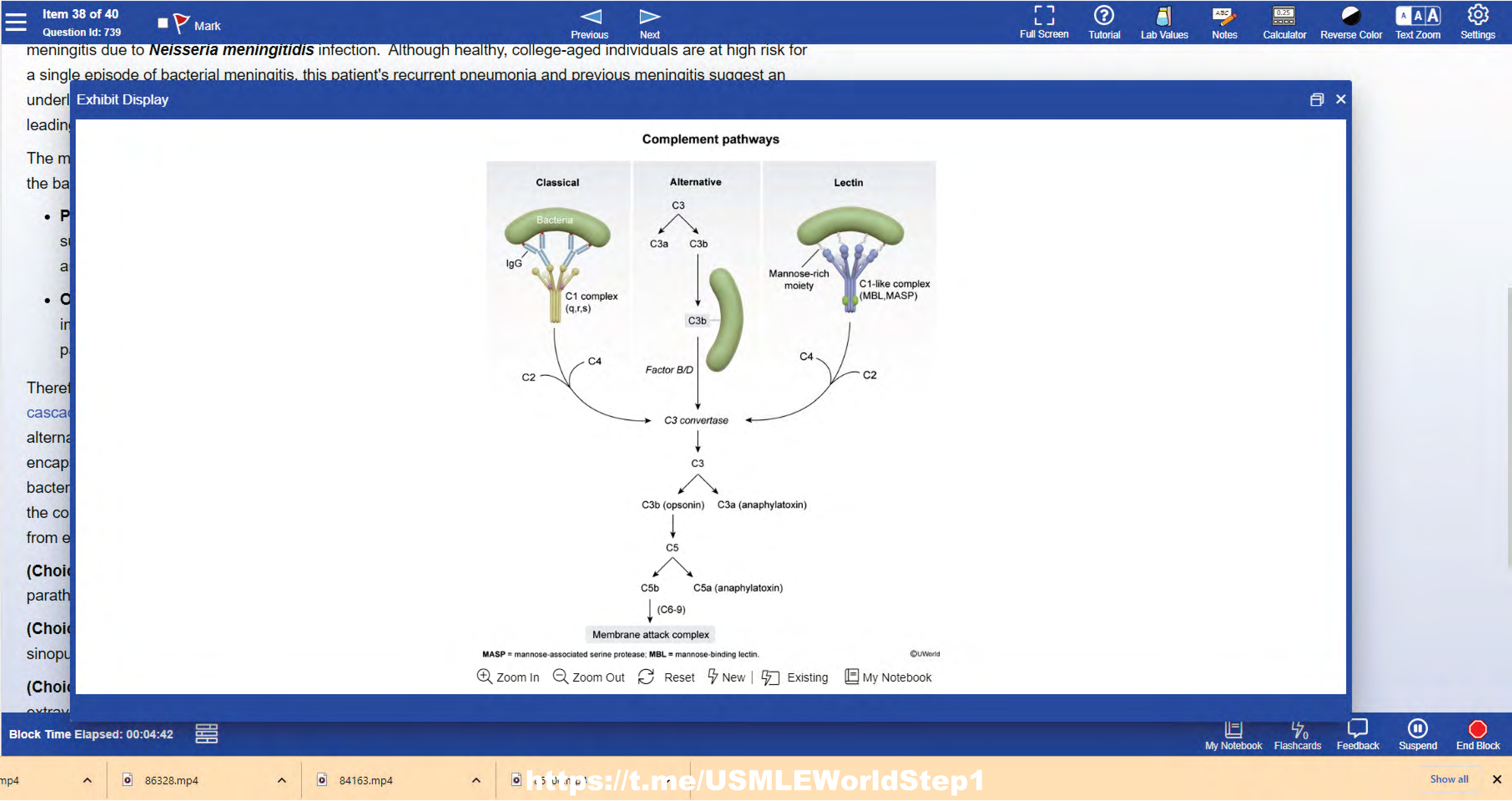
(Choice B) Excessive IgE production is seen in hyperimmunoglobulin E syndrome. Although recurrent sinopulmonary infection is common, patients also have severe eczema and recurrent abscesses.

(Choice C) Impaired neutrophil chemotaxis is seen in leukocyte adhesion defects, which prevent neutrophil extravasation and migration to areas of infection. Although recurrent bacterial infection is common, patients often have a variety of other findings (eg, absence of pus, delayed umbilical cord separation, impaired wound healing).

(Choice E) Chronic granulomatous disease is an X-linked immunodeficiency due to impaired NADPH oxidase, which prevents neutrophils from generating an oxidative burst. Although recurrent pneumonia is common, meningitis is not. In addition, infections associated with this defect are caused by certain catalase-positive organisms (eg, staphylococci), not encapsulated bacteria (eg, *N meningitidis*).

Educational objective:

Deficiency of the complement factors that form the membrane attack complex (C5-C9) results in recurrent infections of the lung and meninges by encapsulated bacteria (eg, *Streptococcus pneumoniae*, *Neisseria meningitidis*).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Factor B/D
Mannose-rich moiety
C1-like complex (MBL,MASP)
C2
C4
C4
C2
C3 convertase
C3
C3b (opsonin)
C3a (anaphylatoxin)
C5
C5b
C5a (anaphylatoxin)
(C6-9)
Membrane attack complex

MASP = mannose-associated serine protease; **MBL** = mannose-binding lectin.

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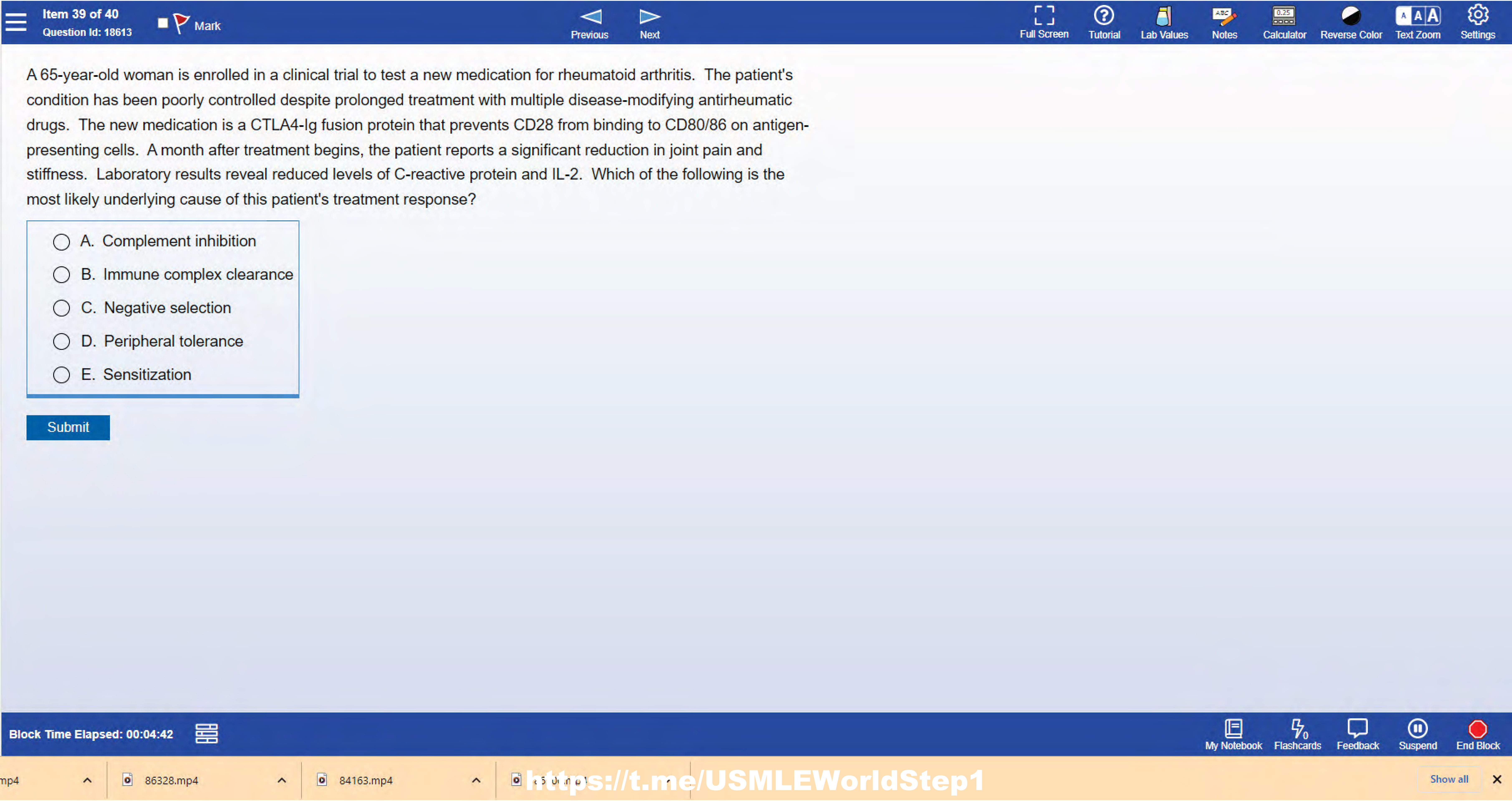
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A 65-year-old woman is enrolled in a clinical trial to test a new medication for rheumatoid arthritis. The patient's condition has been poorly controlled despite prolonged treatment with multiple disease-modifying antirheumatic drugs. The new medication is a CTLA4-Ig fusion protein that prevents CD28 from binding to CD80/86 on antigen-presenting cells. A month after treatment begins, the patient reports a significant reduction in joint pain and stiffness. Laboratory results reveal reduced levels of C-reactive protein and IL-2. Which of the following is the most likely underlying cause of this patient's treatment response?

○ A. Complement inhibition
○ B. Immune complex clearance
○ C. Negative selection
○ D. Peripheral tolerance
○ E. Sensitization

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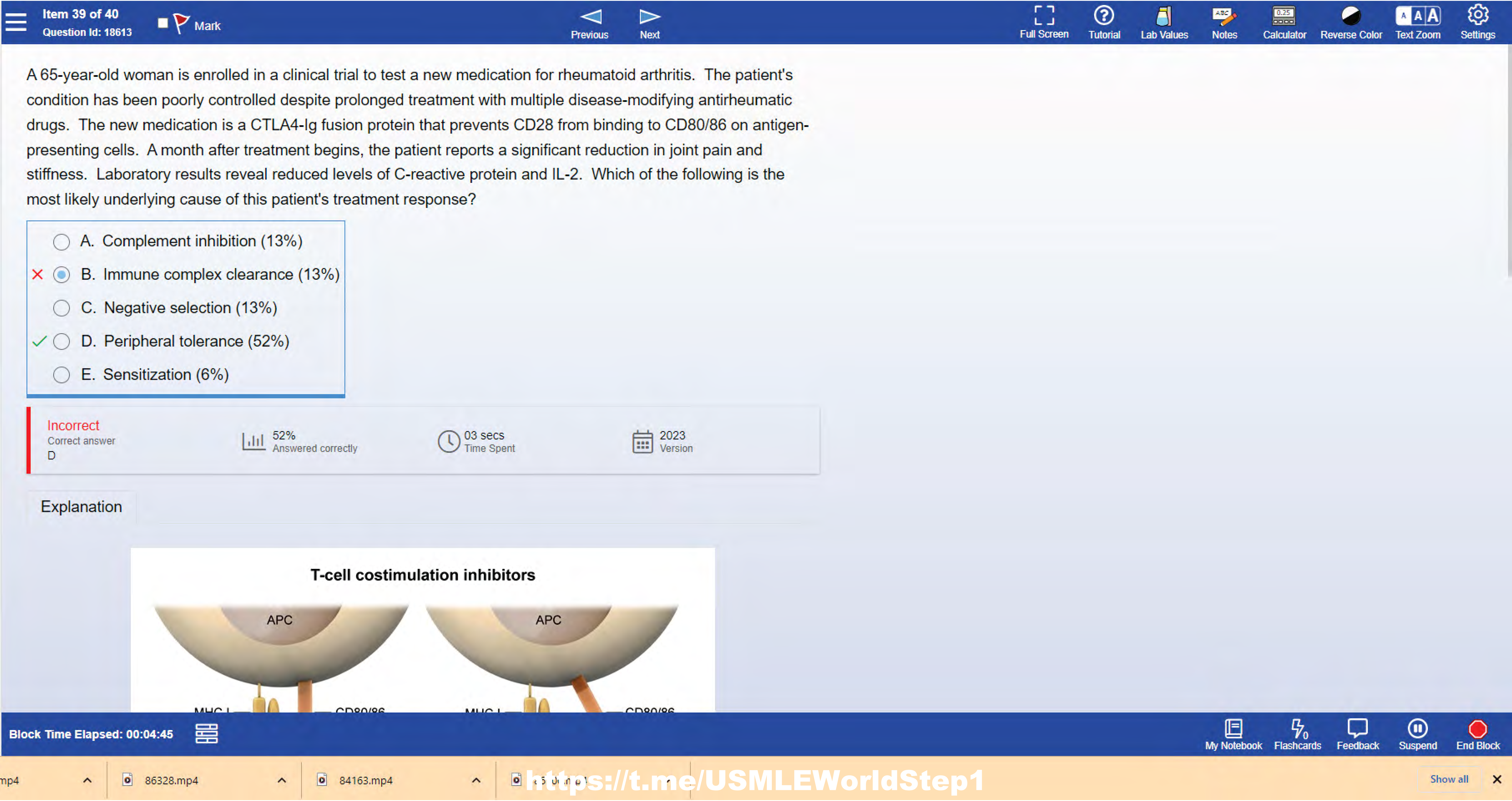

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A 65-year-old woman is enrolled in a clinical trial to test a new medication for rheumatoid arthritis. The patient's condition has been poorly controlled despite prolonged treatment with multiple disease-modifying antirheumatic drugs. The new medication is a CTLA4-Ig fusion protein that prevents CD28 from binding to CD80/86 on antigen-presenting cells. A month after treatment begins, the patient reports a significant reduction in joint pain and stiffness. Laboratory results reveal reduced levels of C-reactive protein and IL-2. Which of the following is the most likely underlying cause of this patient's treatment response?

- ○ A. Complement inhibition (13%)
- ✗ ● B. Immune complex clearance (13%)
- ○ C. Negative selection (13%)
- ✓ ○ D. Peripheral tolerance (52%)
- ○ E. Sensitization (6%)

Incorrect
Correct answer
D

52%
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Explanation

T-cell costimulation inhibitors

APC
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CD80/86
MHC I
CD80/86
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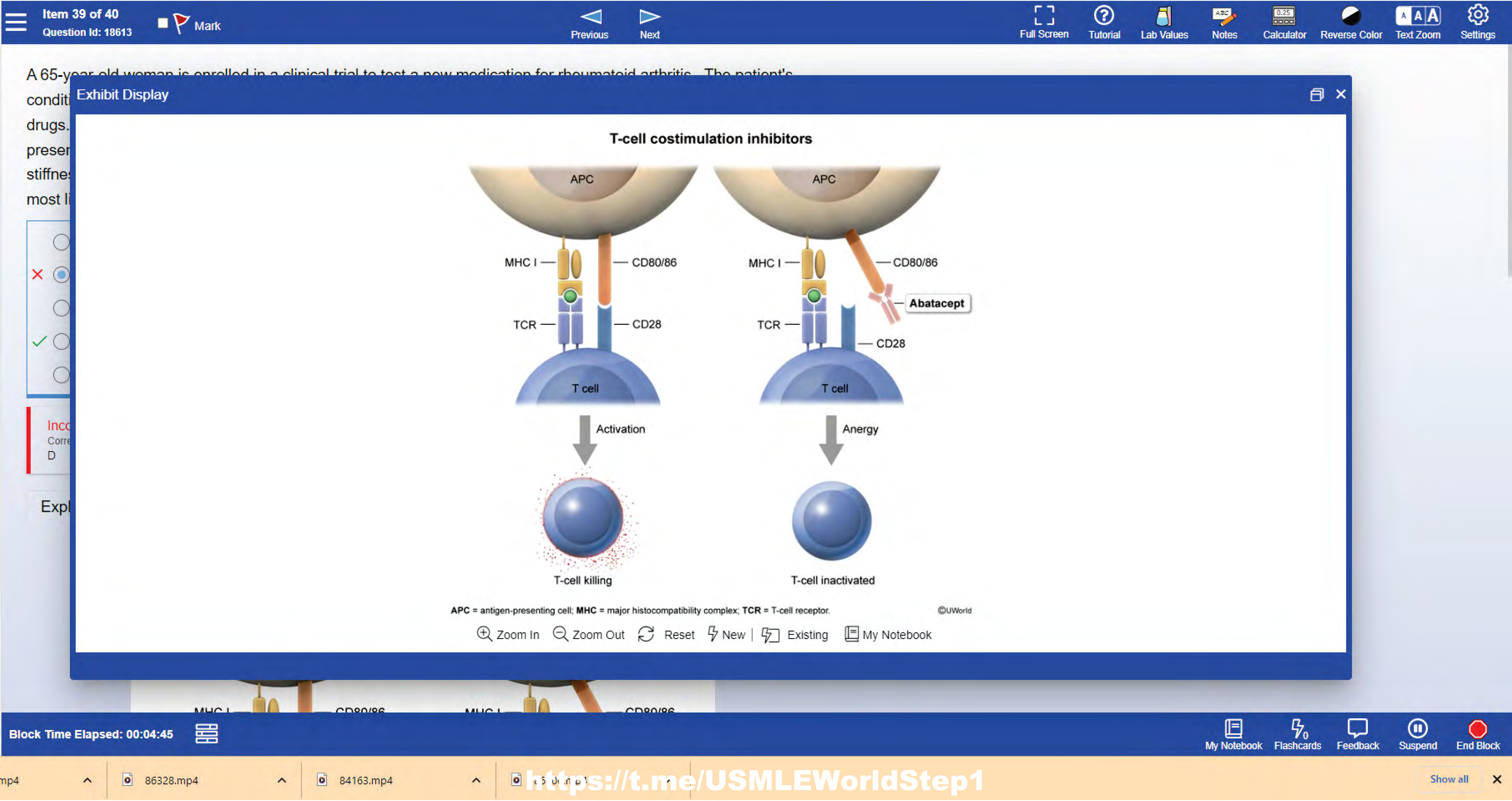
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T-cell costimulation inhibitors

APC
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TCR
CD28
T cell
Activation
T-cell killing
APC
MHC I
CD80/86
Abatacept
TCR
CD28
T cell
Anergy
T-cell inactivated

APC = antigen-presenting cell; **MHC** = major histocompatibility complex; **TCR** = T-cell receptor.

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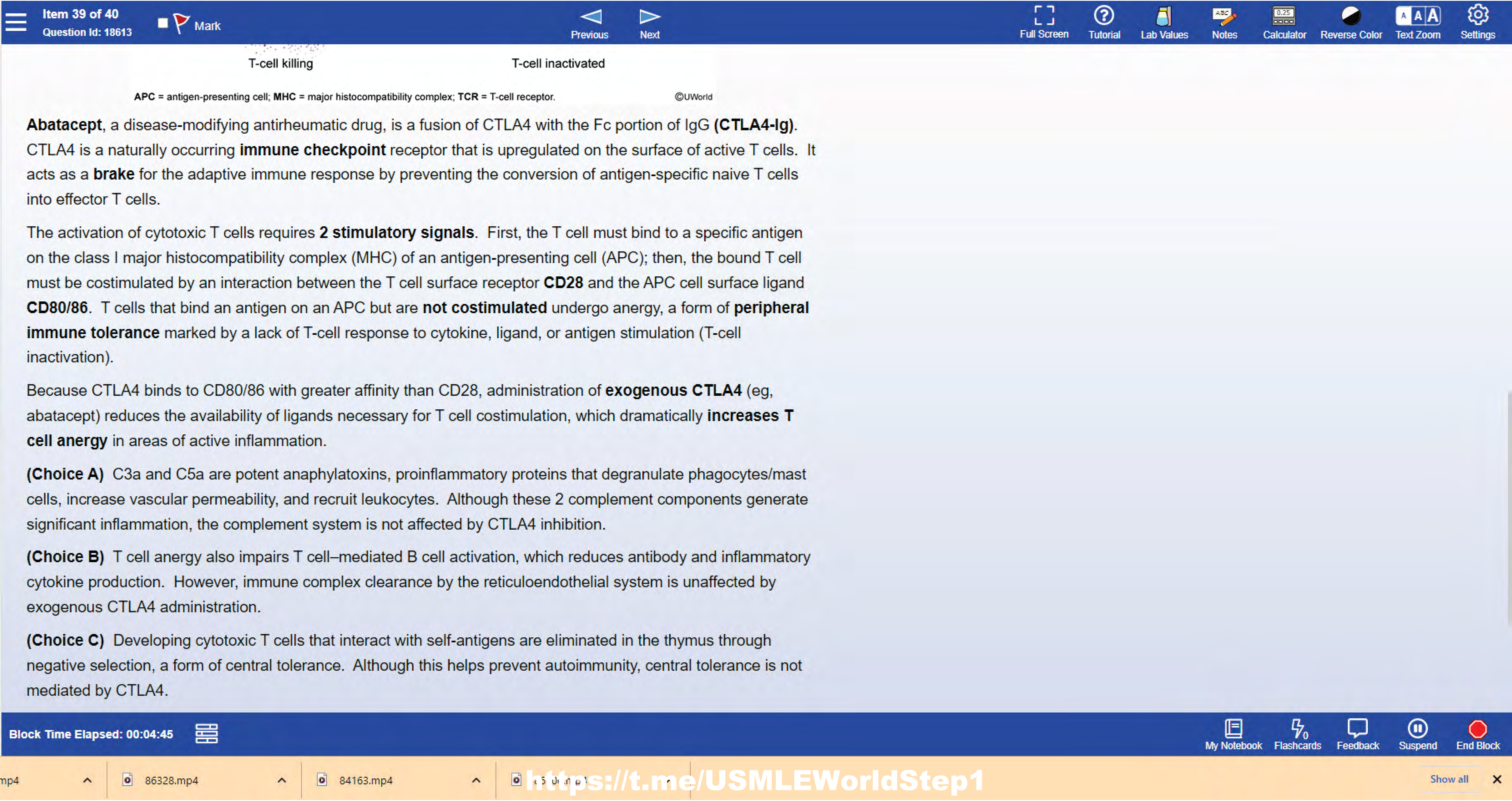
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T-cell killing
T-cell inactivated

APC = antigen-presenting cell; **MHC** = major histocompatibility complex; **TCR** = T-cell receptor. ©UWorld

Abatacept, a disease-modifying antirheumatic drug, is a fusion of CTLA4 with the Fc portion of IgG **(CTLA4-Ig)**. CTLA4 is a naturally occurring **immune checkpoint** receptor that is upregulated on the surface of active T cells. It acts as a **brake** for the adaptive immune response by preventing the conversion of antigen-specific naive T cells into effector T cells.

The activation of cytotoxic T cells requires **2 stimulatory signals**. First, the T cell must bind to a specific antigen on the class I major histocompatibility complex (MHC) of an antigen-presenting cell (APC); then, the bound T cell must be costimulated by an interaction between the T cell surface receptor **CD28** and the APC cell surface ligand **CD80/86**. T cells that bind an antigen on an APC but are **not costimulated** undergo anergy, a form of **peripheral immune tolerance** marked by a lack of T-cell response to cytokine, ligand, or antigen stimulation (T-cell inactivation).

Because CTLA4 binds to CD80/86 with greater affinity than CD28, administration of **exogenous CTLA4** (eg, abatacept) reduces the availability of ligands necessary for T cell costimulation, which dramatically **increases T cell anergy** in areas of active inflammation.

(Choice A) C3a and C5a are potent anaphylatoxins, proinflammatory proteins that degranulate phagocytes/mast cells, increase vascular permeability, and recruit leukocytes. Although these 2 complement components generate significant inflammation, the complement system is not affected by CTLA4 inhibition.

(Choice B) T cell anergy also impairs T cell–mediated B cell activation, which reduces antibody and inflammatory cytokine production. However, immune complex clearance by the reticuloendothelial system is unaffected by exogenous CTLA4 administration.

(Choice C) Developing cytotoxic T cells that interact with self-antigens are eliminated in the thymus through negative selection, a form of central tolerance. Although this helps prevent autoimmunity, central tolerance is not mediated by CTLA4.

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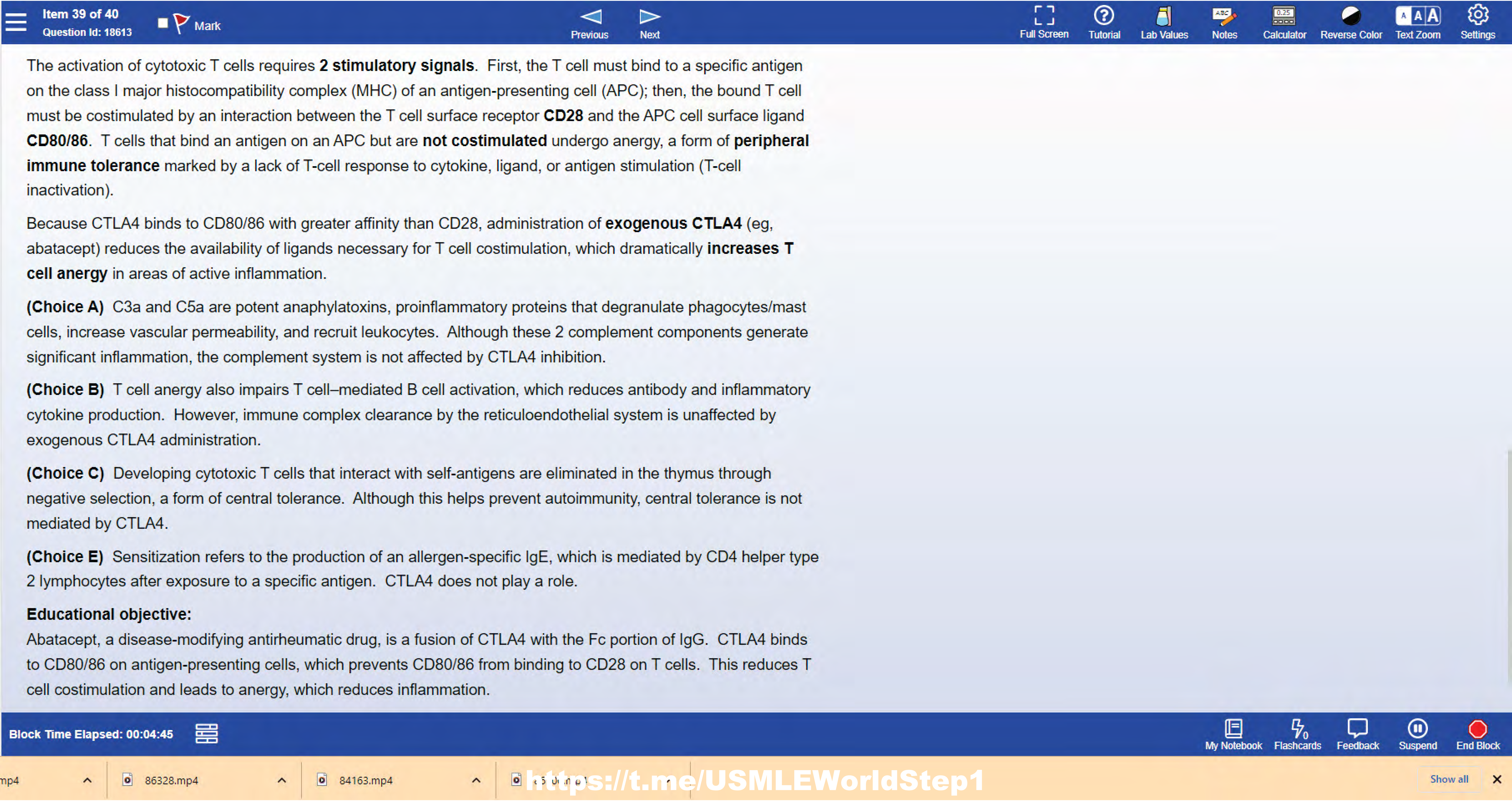

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(Choice C) Developing cytotoxic T cells that interact with self-antigens are eliminated in the thymus through negative selection, a form of central tolerance. Although this helps prevent autoimmunity, central tolerance is not mediated by CTLA4.

(Choice E) Sensitization refers to the production of an allergen-specific IgE, which is mediated by CD4 helper type 2 lymphocytes after exposure to a specific antigen. CTLA4 does not play a role.

Educational objective:

Abatacept, a disease-modifying antirheumatic drug, is a fusion of CTLA4 with the Fc portion of IgG. CTLA4 binds to CD80/86 on antigen-presenting cells, which prevents CD80/86 from binding to CD28 on T cells. This reduces T cell costimulation and leads to anergy, which reduces inflammation.

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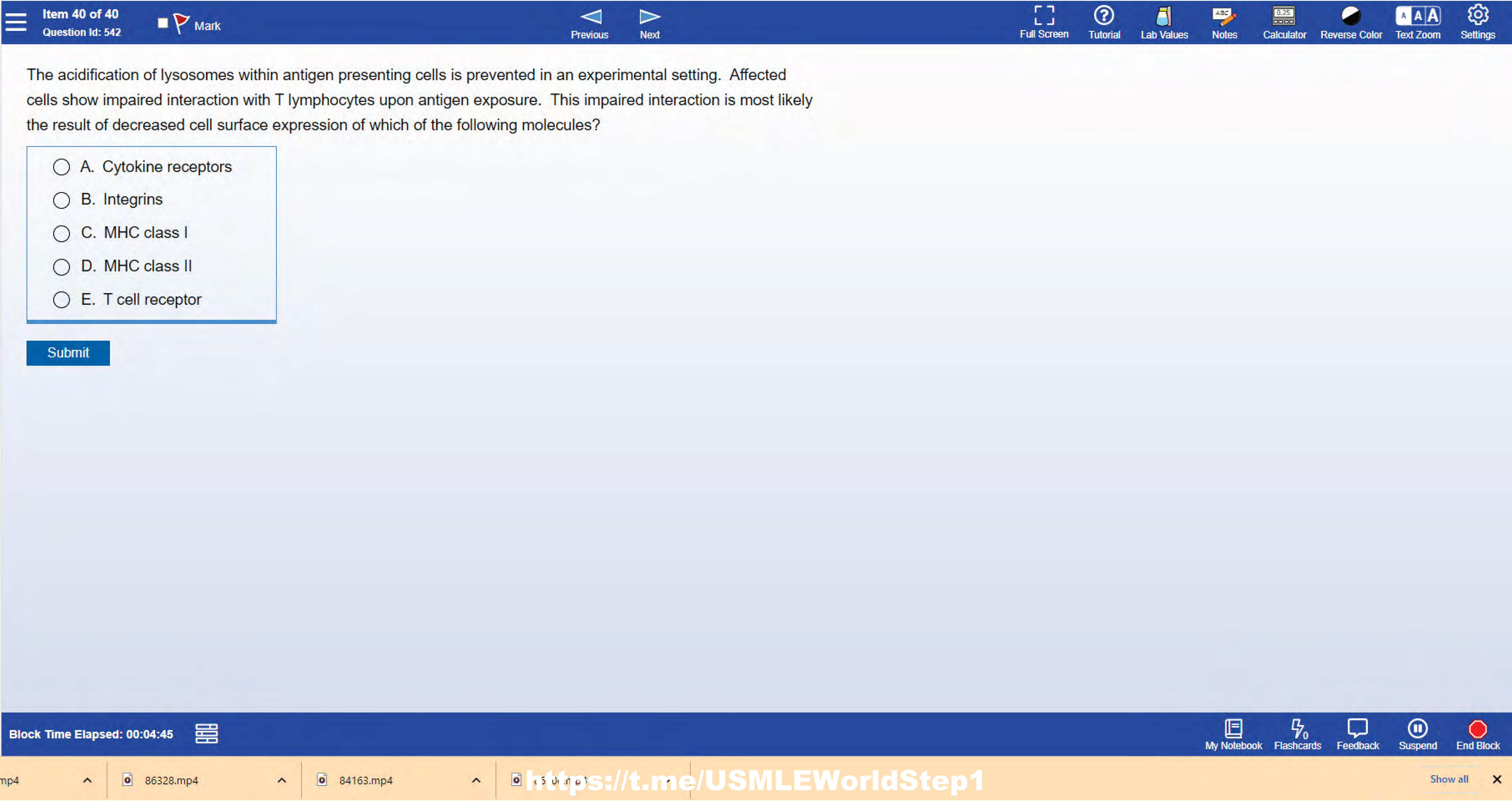
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The acidification of lysosomes within antigen presenting cells is prevented in an experimental setting. Affected cells show impaired interaction with T lymphocytes upon antigen exposure. This impaired interaction is most likely the result of decreased cell surface expression of which of the following molecules?

○ A. Cytokine receptors
○ B. Integrins
○ C. MHC class I
○ D. MHC class II
○ E. T cell receptor

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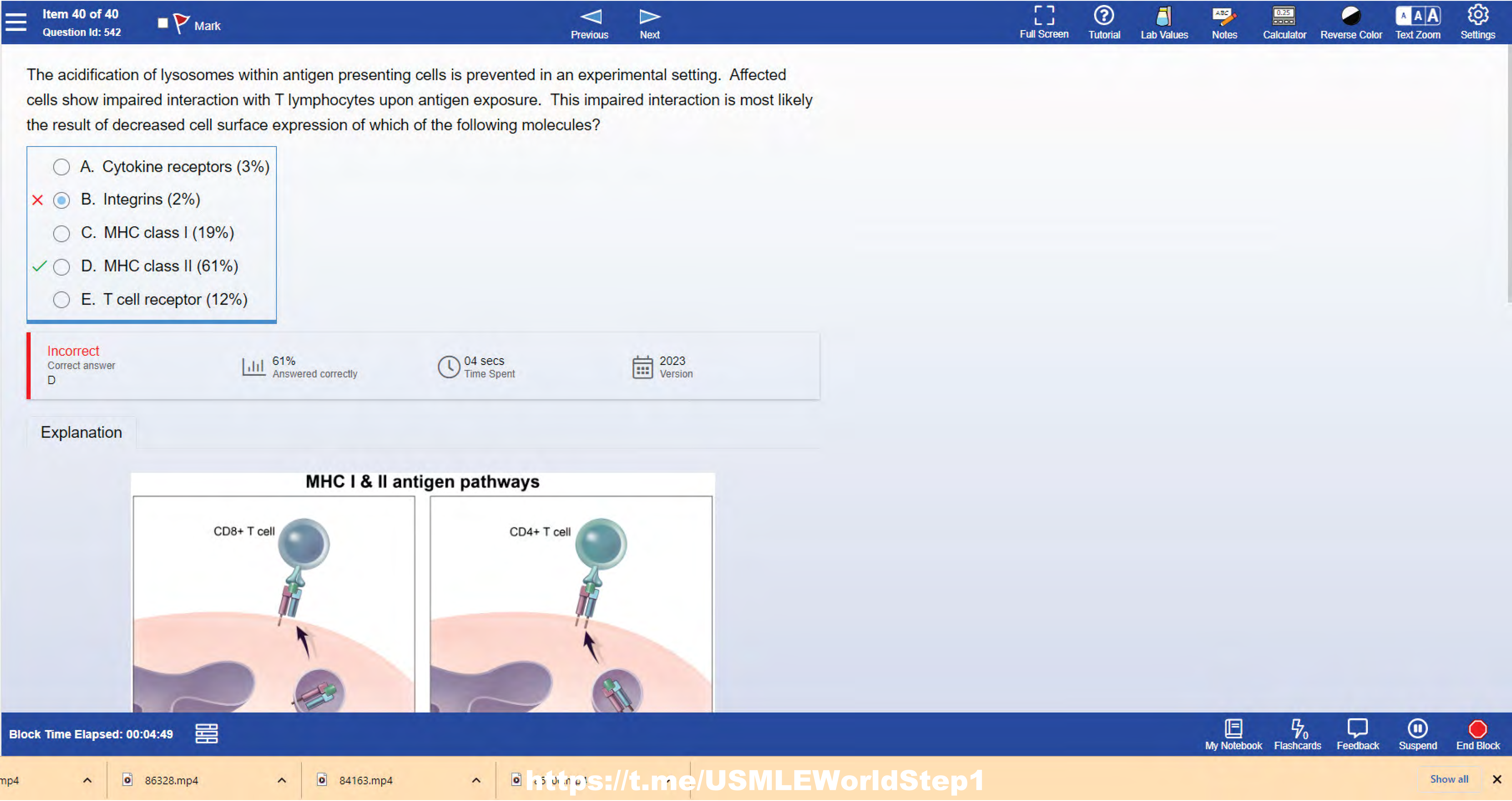
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Question Id: 542
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Settings

The acidification of lysosomes within antigen presenting cells is prevented in an experimental setting. Affected cells show impaired interaction with T lymphocytes upon antigen exposure. This impaired interaction is most likely the result of decreased cell surface expression of which of the following molecules?

- ○ A. Cytokine receptors (3%)
- ✗ ● B. Integrins (2%)
- ○ C. MHC class I (19%)
- ✓ ○ D. MHC class II (61%)
- ○ E. T cell receptor (12%)

Incorrect
Correct answer
D

61%
Answered correctly

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Version

Explanation

MHC I & II antigen pathways

CD8+ T cell
CD4+ T cell
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the result of decreased cell surface expression of which of the following molecules?

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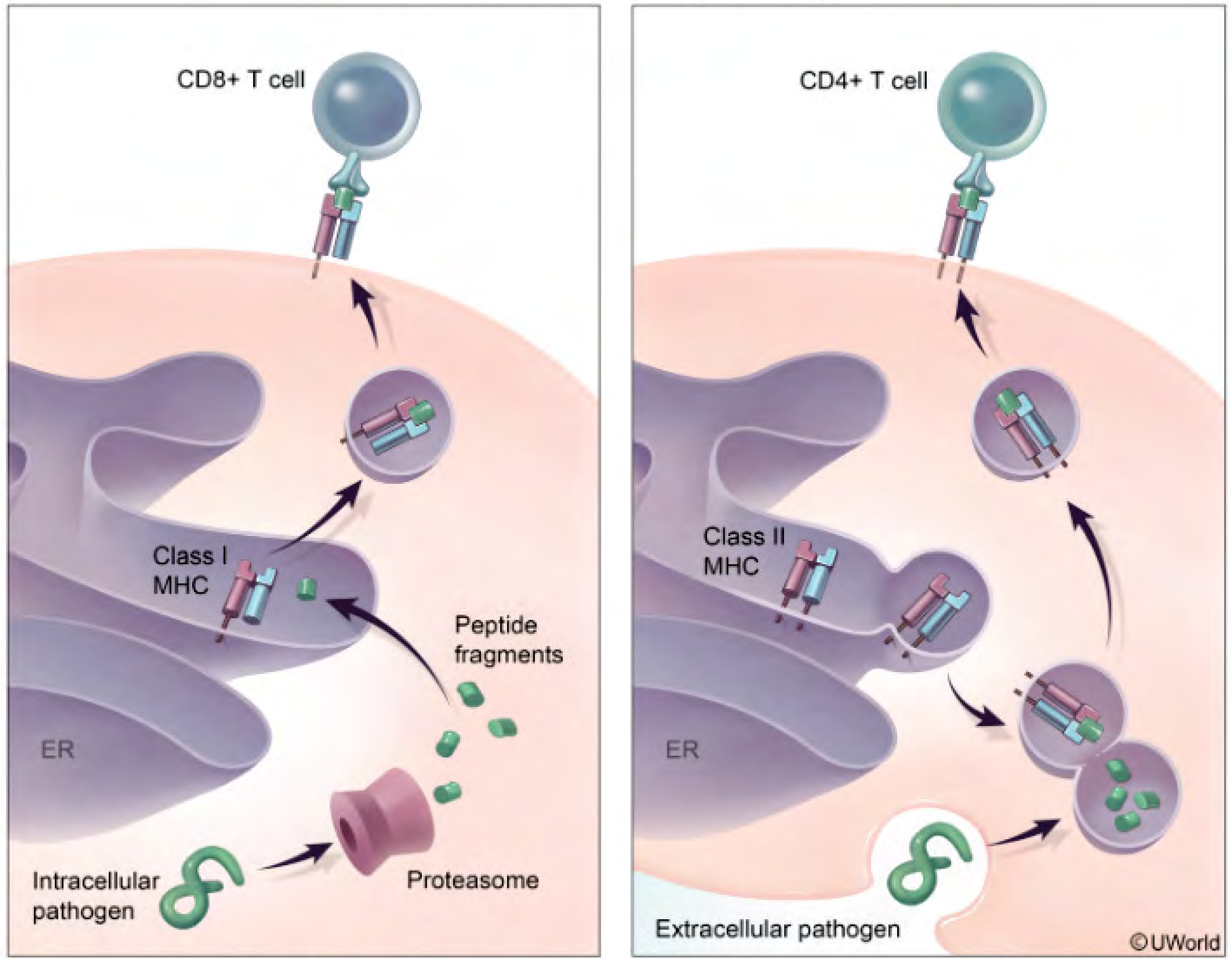
MHC I & II antigen pathways


CD8+ T cell
Class I MHC
Peptide fragments
ER
Intracellular pathogen
Proteasome
CD4+ T cell
Class II MHC
ER
Extracellular pathogen
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Class I MHC pathway **Class II MHC pathway**

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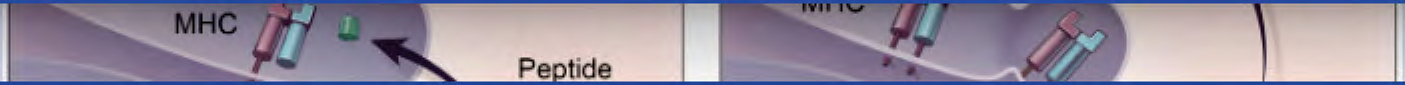
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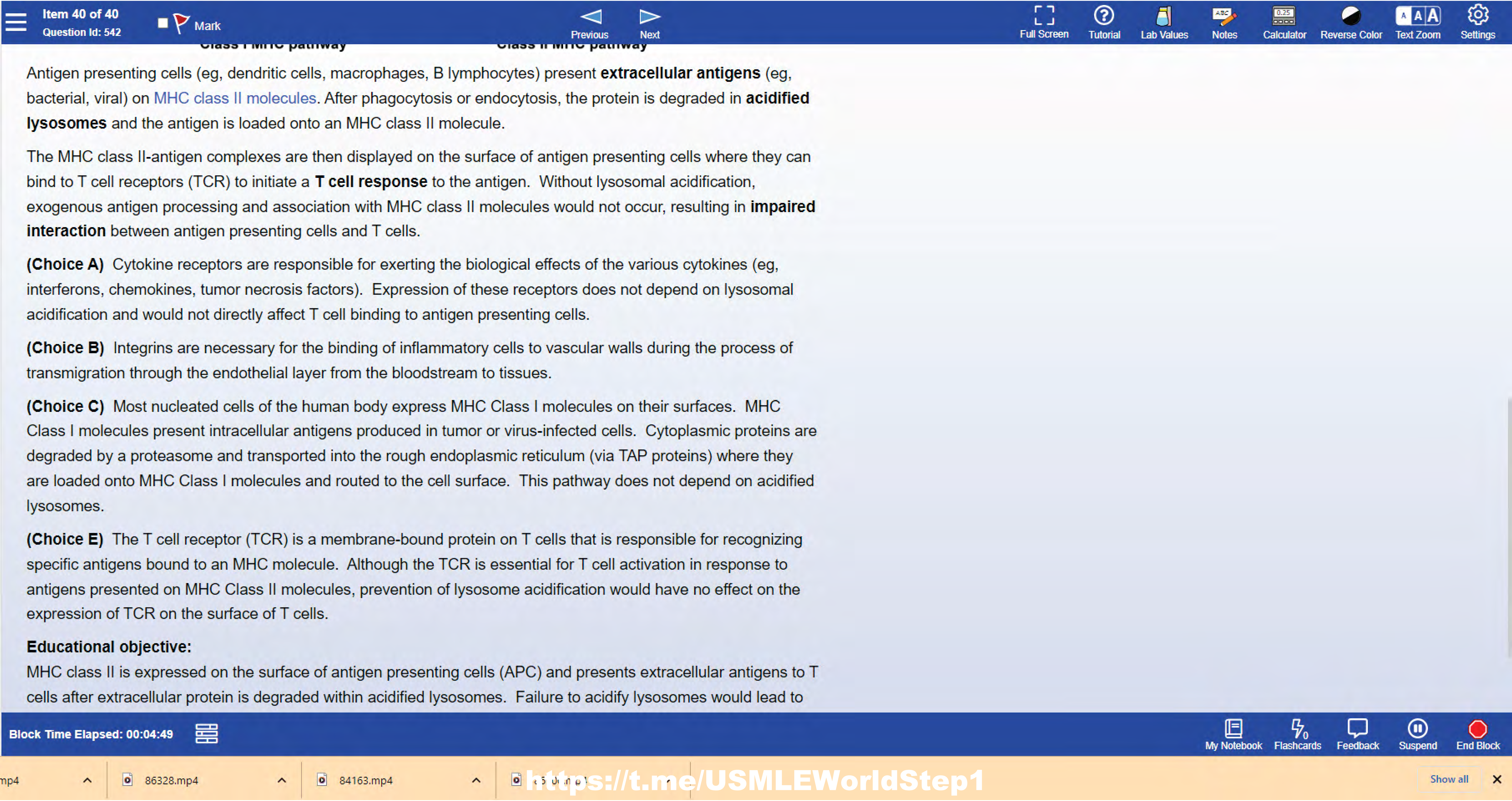

Antigen presenting cells (eg, dendritic cells, macrophages, B lymphocytes) present **extracellular antigens** (eg, bacterial, viral) on MHC class II molecules. After phagocytosis or endocytosis, the protein is degraded in **acidified lysosomes** and the antigen is loaded onto an MHC class II molecule.

The MHC class II-antigen complexes are then displayed on the surface of antigen presenting cells where they can bind to T cell receptors (TCR) to initiate a **T cell response** to the antigen. Without lysosomal acidification, exogenous antigen processing and association with MHC class II molecules would not occur, resulting in **impaired interaction** between antigen presenting cells and T cells.

(Choice A) Cytokine receptors are responsible for exerting the biological effects of the various cytokines (eg, interferons, chemokines, tumor necrosis factors). Expression of these receptors does not depend on lysosomal acidification and would not directly affect T cell binding to antigen presenting cells.

(Choice B) Integrins are necessary for the binding of inflammatory cells to vascular walls during the process of transmigration through the endothelial layer from the bloodstream to tissues.

(Choice C) Most nucleated cells of the human body express MHC Class I molecules on their surfaces. MHC Class I molecules present intracellular antigens produced in tumor or virus-infected cells. Cytoplasmic proteins are degraded by a proteasome and transported into the rough endoplasmic reticulum (via TAP proteins) where they are loaded onto MHC Class I molecules and routed to the cell surface. This pathway does not depend on acidified lysosomes.

(Choice E) The T cell receptor (TCR) is a membrane-bound protein on T cells that is responsible for recognizing specific antigens bound to an MHC molecule. Although the TCR is essential for T cell activation in response to antigens presented on MHC Class II molecules, prevention of lysosome acidification would have no effect on the expression of TCR on the surface of T cells.

Educational objective:

MHC class II is expressed on the surface of antigen presenting cells (APC) and presents extracellular antigens to T cells after extracellular protein is degraded within acidified lysosomes. Failure to acidify lysosomes would lead to

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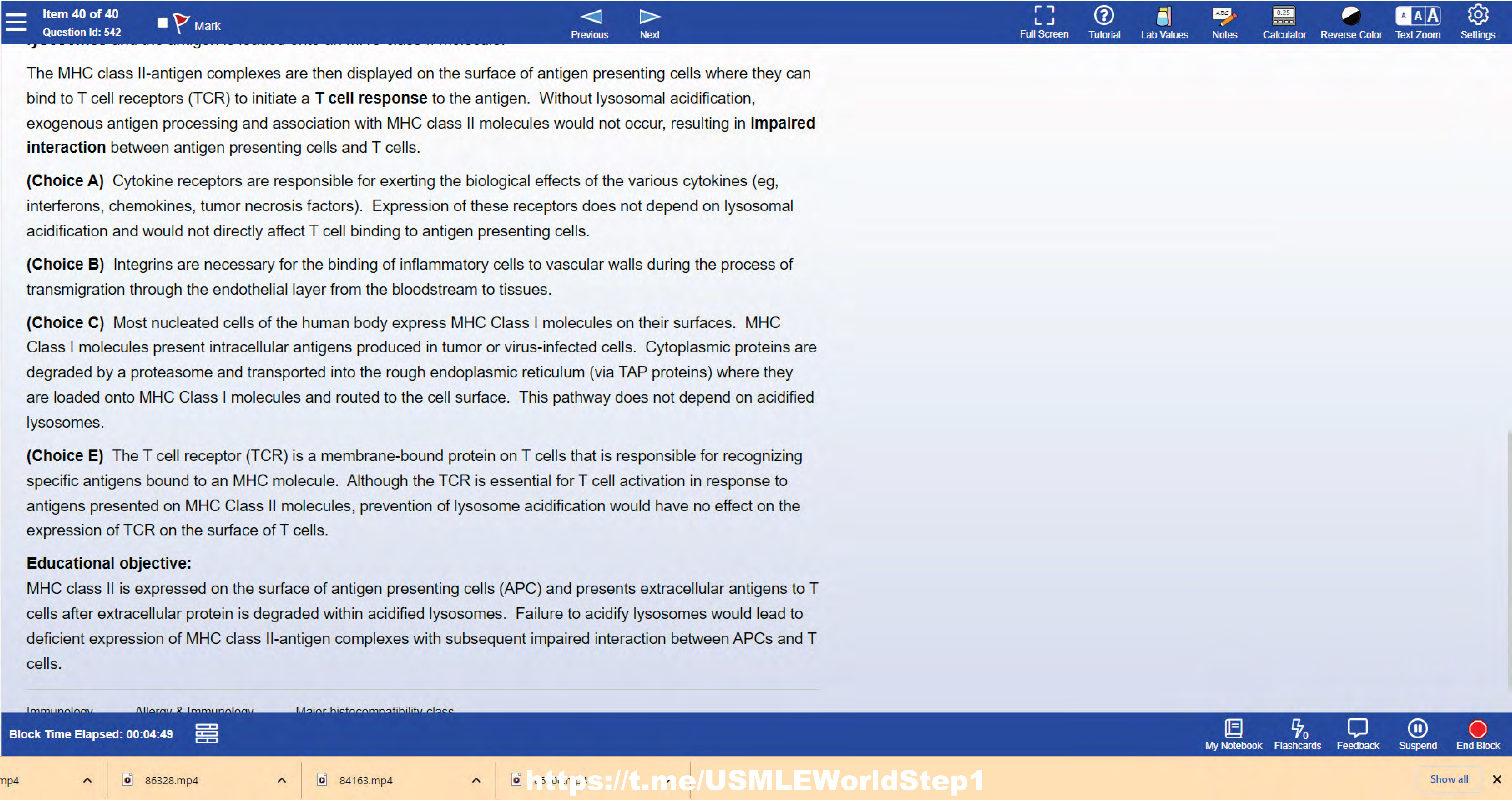
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Educational objective:

MHC class II is expressed on the surface of antigen presenting cells (APC) and presents extracellular antigens to T cells after extracellular protein is degraded within acidified lysosomes. Failure to acidify lysosomes would lead to deficient expression of MHC class II-antigen complexes with subsequent impaired interaction between APCs and T cells.

Immunology
Allergy & Immunology
Major histocompatibility class
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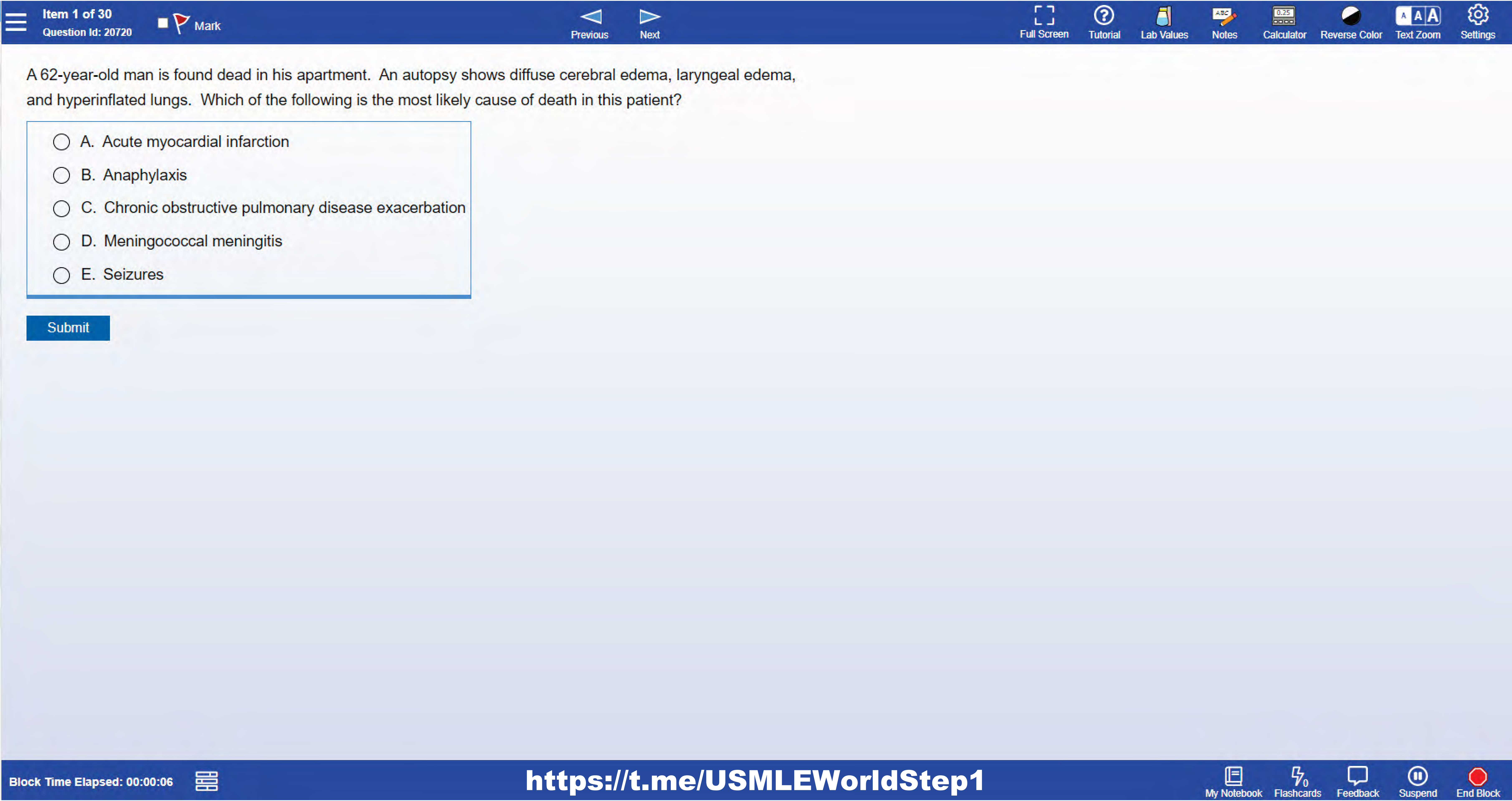
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A 62-year-old man is found dead in his apartment. An autopsy shows diffuse cerebral edema, laryngeal edema, and hyperinflated lungs. Which of the following is the most likely cause of death in this patient?

○ A. Acute myocardial infarction
○ B. Anaphylaxis
○ C. Chronic obstructive pulmonary disease exacerbation
○ D. Meningococcal meningitis
○ E. Seizures

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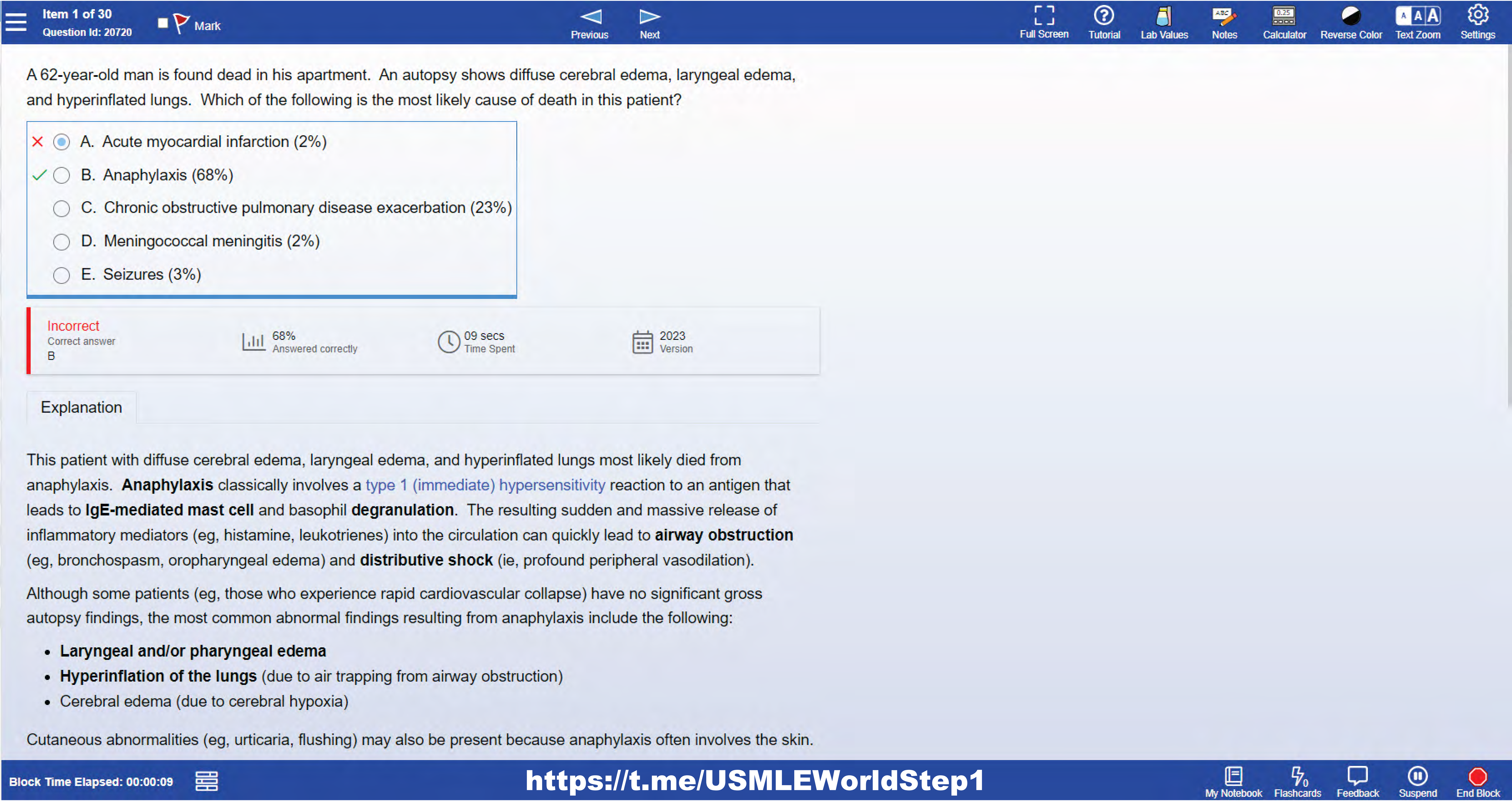
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A 62-year-old man is found dead in his apartment. An autopsy shows diffuse cerebral edema, laryngeal edema, and hyperinflated lungs. Which of the following is the most likely cause of death in this patient?

✗ ● A. Acute myocardial infarction (2%)

✓ ○ B. Anaphylaxis (68%)

○ C. Chronic obstructive pulmonary disease exacerbation (23%)

○ D. Meningococcal meningitis (2%)

○ E. Seizures (3%)

Incorrect
Correct answer
B

68%
Answered correctly

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Explanation

This patient with diffuse cerebral edema, laryngeal edema, and hyperinflated lungs most likely died from anaphylaxis. **Anaphylaxis** classically involves a type 1 (immediate) hypersensitivity reaction to an antigen that leads to **IgE-mediated mast cell** and basophil **degranulation**. The resulting sudden and massive release of inflammatory mediators (eg, histamine, leukotrienes) into the circulation can quickly lead to **airway obstruction** (eg, bronchospasm, oropharyngeal edema) and **distributive shock** (ie, profound peripheral vasodilation).

Although some patients (eg, those who experience rapid cardiovascular collapse) have no significant gross autopsy findings, the most common abnormal findings resulting from anaphylaxis include the following:

- **Laryngeal and/or pharyngeal edema**
- **Hyperinflation of the lungs** (due to air trapping from airway obstruction)
- Cerebral edema (due to cerebral hypoxia)

Cutaneous abnormalities (eg, urticaria, flushing) may also be present because anaphylaxis often involves the skin.

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- Cerebral edema (due to cerebral hypoxia)

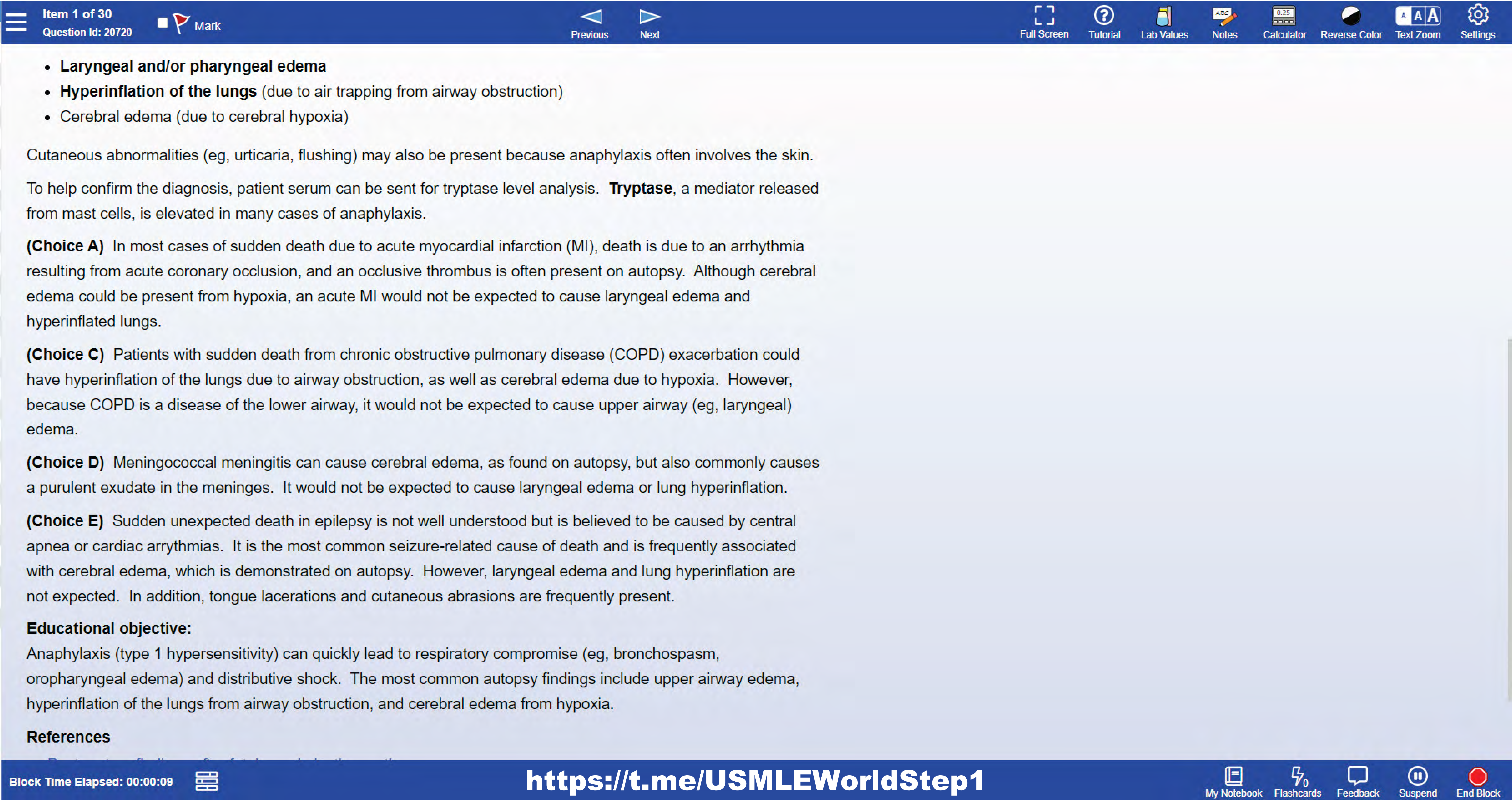
Cutaneous abnormalities (eg, urticaria, flushing) may also be present because anaphylaxis often involves the skin.

To help confirm the diagnosis, patient serum can be sent for tryptase level analysis. **Tryptase**, a mediator released from mast cells, is elevated in many cases of anaphylaxis.

(Choice A) In most cases of sudden death due to acute myocardial infarction (MI), death is due to an arrhythmia resulting from acute coronary occlusion, and an occlusive thrombus is often present on autopsy. Although cerebral edema could be present from hypoxia, an acute MI would not be expected to cause laryngeal edema and hyperinflated lungs.

(Choice C) Patients with sudden death from chronic obstructive pulmonary disease (COPD) exacerbation could have hyperinflation of the lungs due to airway obstruction, as well as cerebral edema due to hypoxia. However, because COPD is a disease of the lower airway, it would not be expected to cause upper airway (eg, laryngeal) edema.

(Choice D) Meningococcal meningitis can cause cerebral edema, as found on autopsy, but also commonly causes a purulent exudate in the meninges. It would not be expected to cause laryngeal edema or lung hyperinflation.



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(Choice D) Meningococcal meningitis can cause cerebral edema, as found on autopsy, but also commonly causes a purulent exudate in the meninges. It would not be expected to cause laryngeal edema or lung hyperinflation.

(Choice E) Sudden unexpected death in epilepsy is not well understood but is believed to be caused by central apnea or cardiac arrythmias. It is the most common seizure-related cause of death and is frequently associated with cerebral edema, which is demonstrated on autopsy. However, laryngeal edema and lung hyperinflation are not expected. In addition, tongue lacerations and cutaneous abrasions are frequently present.

Educational objective:
Anaphylaxis (type 1 hypersensitivity) can quickly lead to respiratory compromise (eg, bronchospasm, oropharyngeal edema) and distributive shock. The most common autopsy findings include upper airway edema, hyperinflation of the lungs from airway obstruction, and cerebral edema from hypoxia.

References

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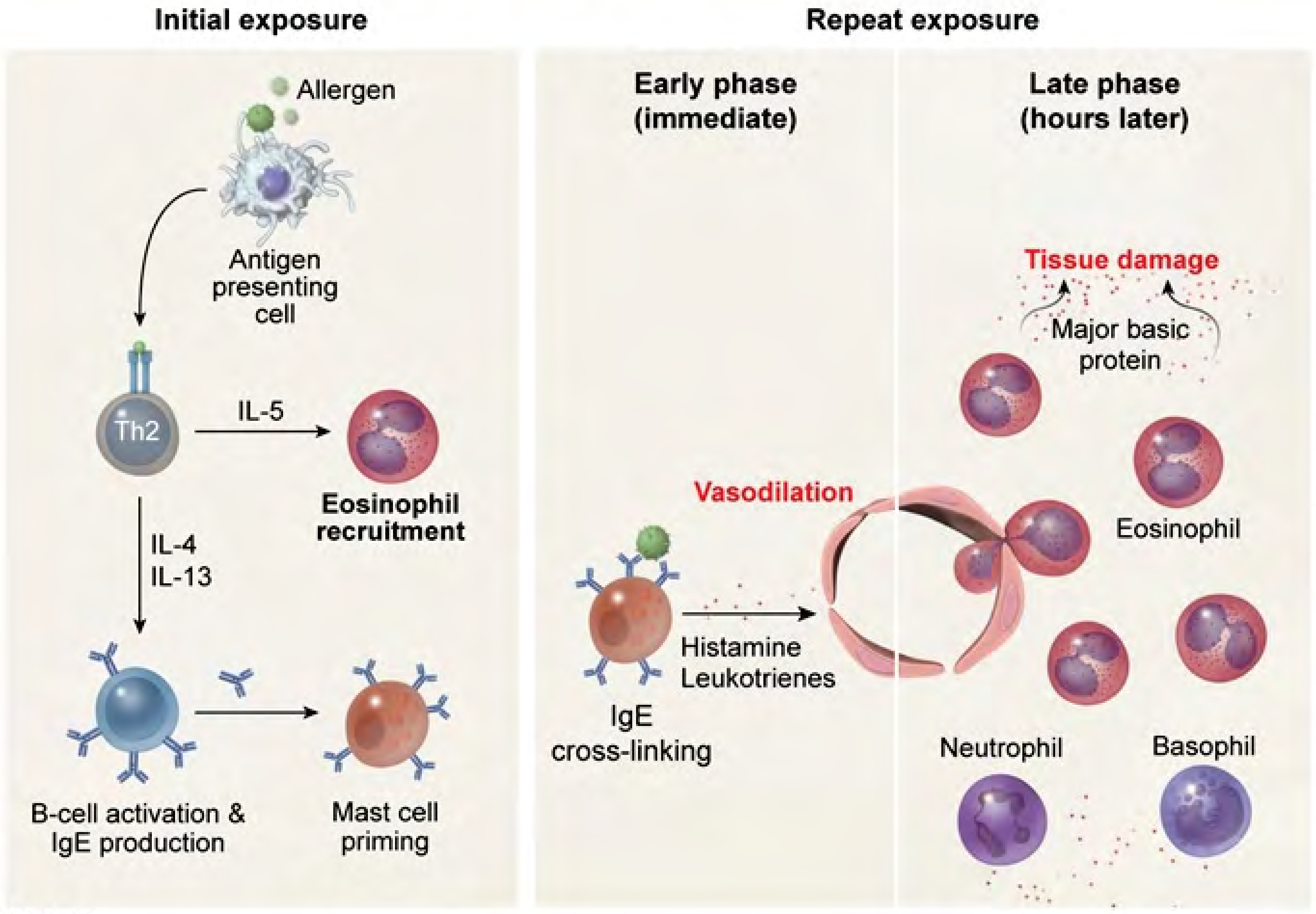
Type 1 hypersensitivity reaction


Initial exposure
Repeat exposure
Allergen
Antigen presenting cell
Th2
IL-5
Eosinophil recruitment
IL-4
IL-13
B-cell activation & IgE production
Mast cell priming
Early phase (immediate)
Late phase (hours later)
Tissue damage
Major basic protein
Vasodilation
Eosinophil
IgE cross-linking
Histamine
Leukotrienes
Neutrophil
Basophil

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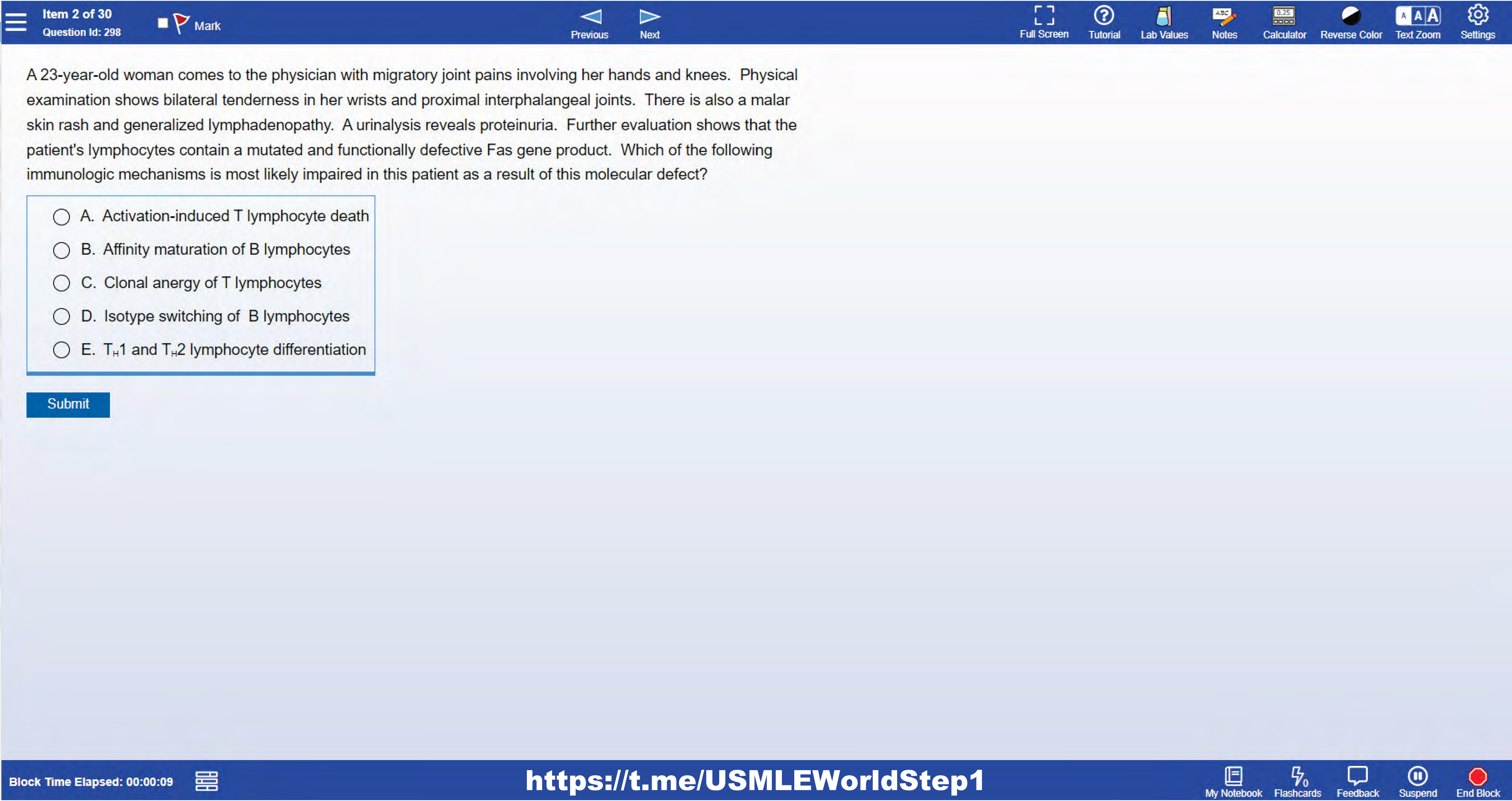
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A 23-year-old woman comes to the physician with migratory joint pains involving her hands and knees. Physical examination shows bilateral tenderness in her wrists and proximal interphalangeal joints. There is also a malar skin rash and generalized lymphadenopathy. A urinalysis reveals proteinuria. Further evaluation shows that the patient's lymphocytes contain a mutated and functionally defective Fas gene product. Which of the following immunologic mechanisms is most likely impaired in this patient as a result of this molecular defect?

○ A. Activation-induced T lymphocyte death

○ B. Affinity maturation of B lymphocytes

○ C. Clonal anergy of T lymphocytes

○ D. Isotype switching of B lymphocytes

○ E. T_H1 and T_H2 lymphocyte differentiation

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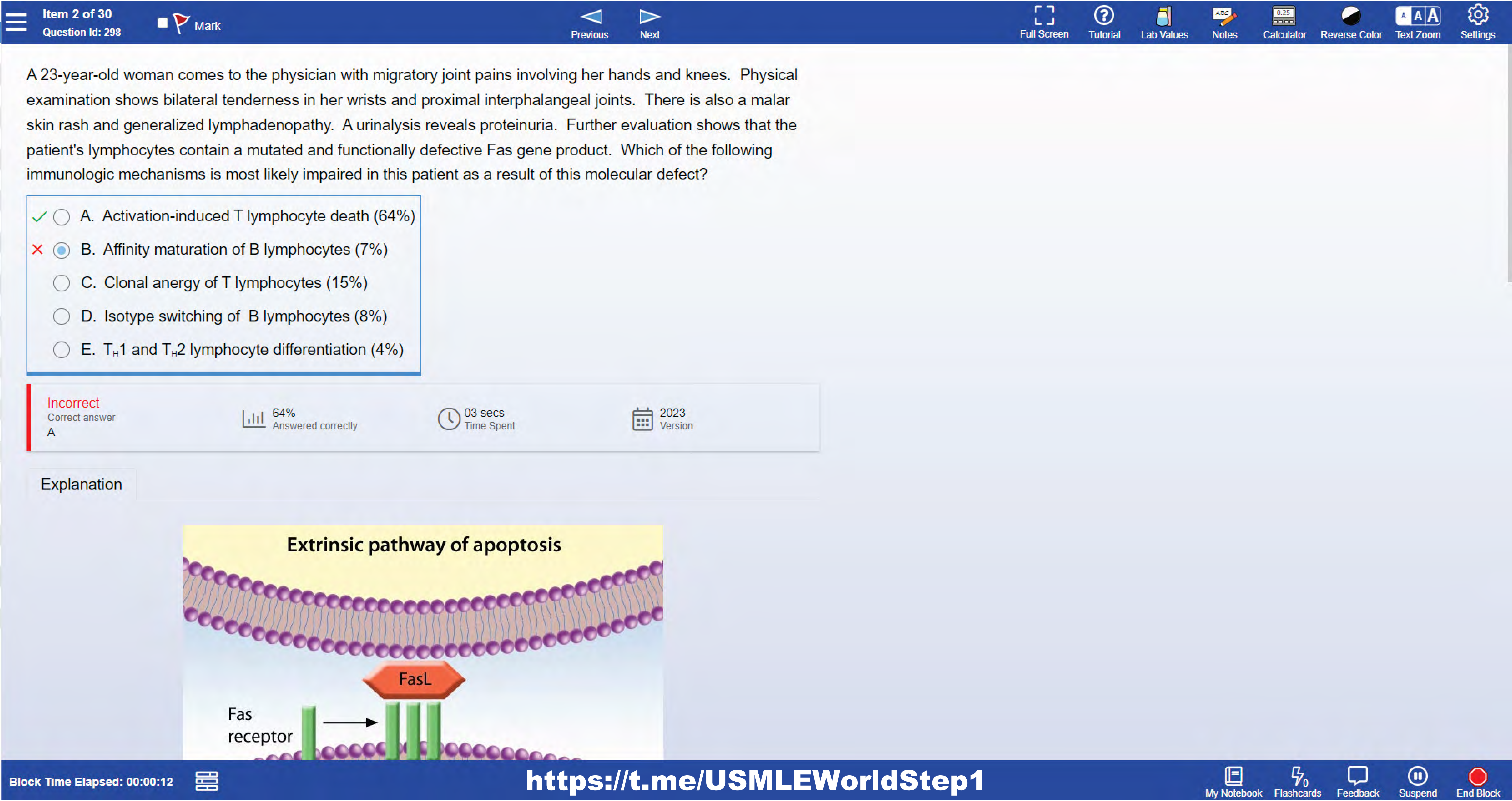
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- ✓ ○ A. Activation-induced T lymphocyte death (64%)
- ✗ ● B. Affinity maturation of B lymphocytes (7%)
- ○ C. Clonal anergy of T lymphocytes (15%)
- ○ D. Isotype switching of B lymphocytes (8%)
- ○ E. T_H1 and T_H2 lymphocyte differentiation (4%)

Incorrect
Correct answer
A

64%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

Extrinsic pathway of apoptosis

FasL
Fas
receptor
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A 23-year-old woman comes to the physician with migratory joint pains involving her hands and knees. Physical
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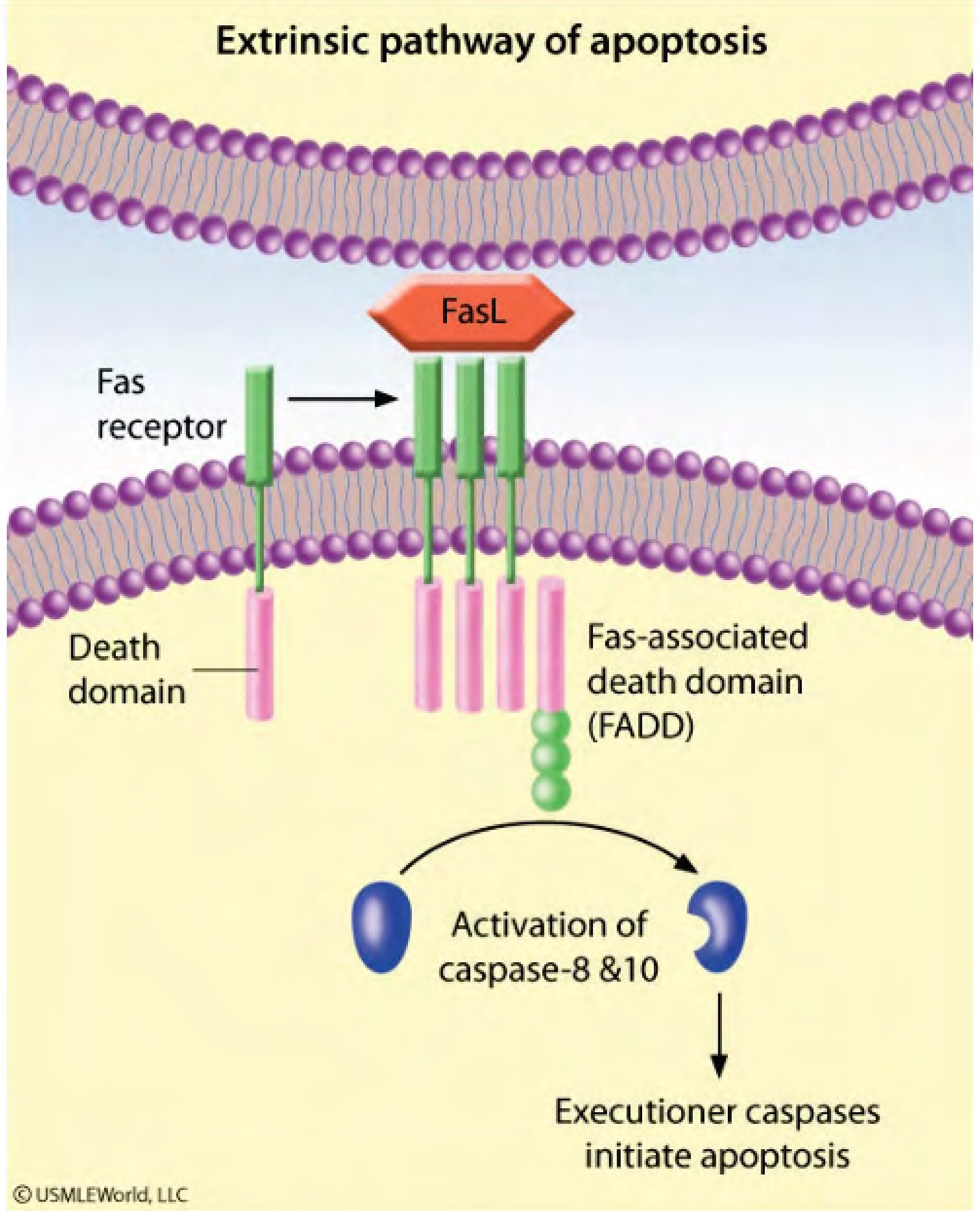
Extrinsic pathway of apoptosis
FasL
Fas receptor
Death domain
Fas-associated death domain (FADD)
Activation of caspase-8 &10
Executioner caspases initiate apoptosis
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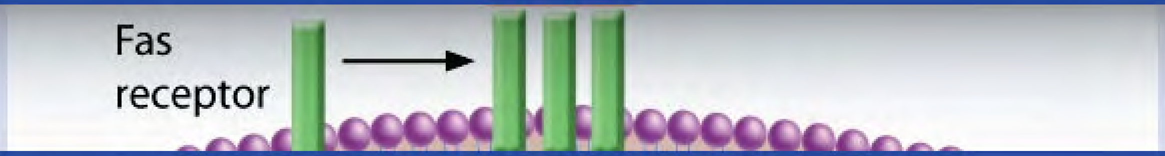
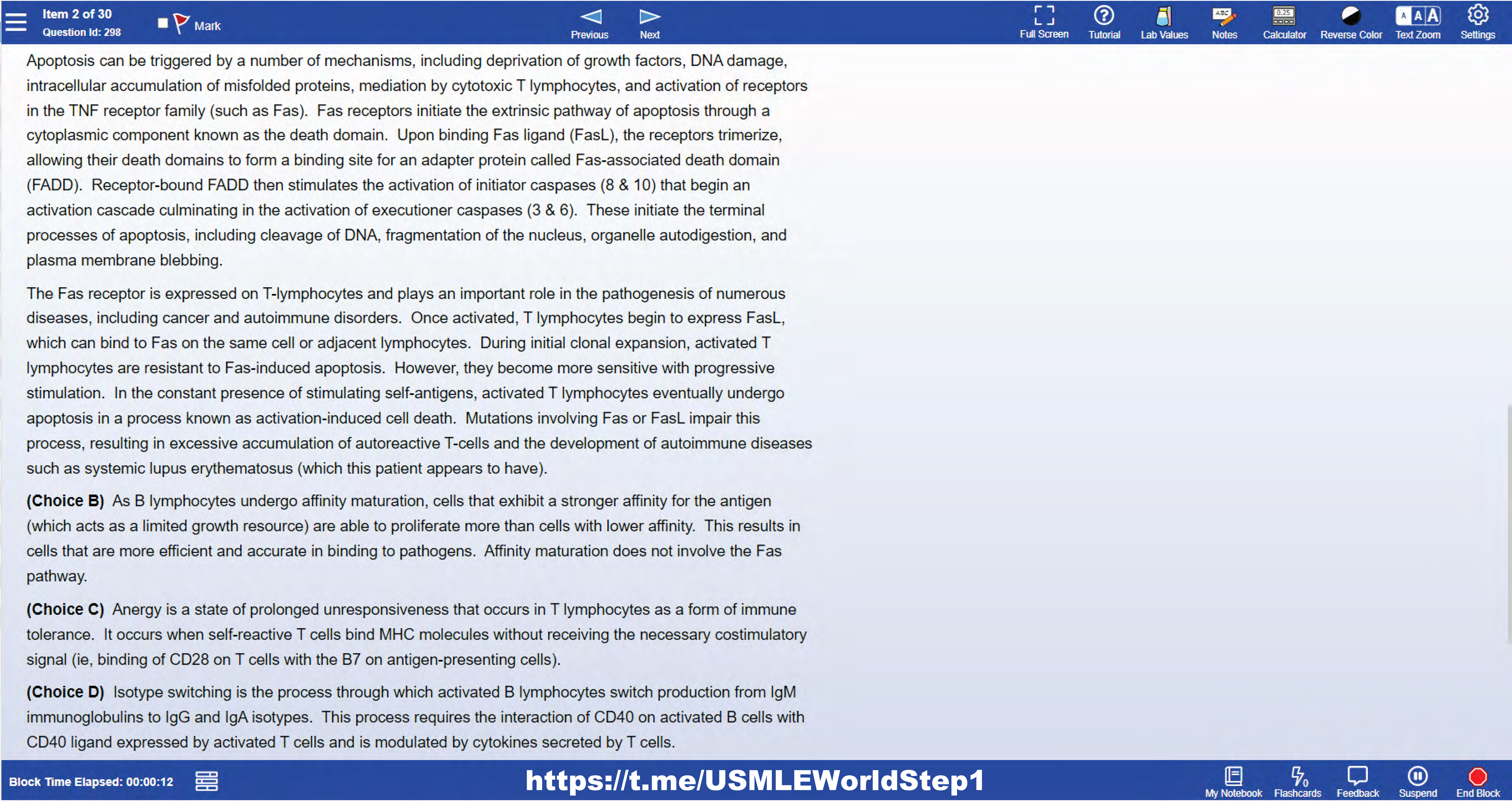

Fas receptor



Apoptosis can be triggered by a number of mechanisms, including deprivation of growth factors, DNA damage, intracellular accumulation of misfolded proteins, mediation by cytotoxic T lymphocytes, and activation of receptors in the TNF receptor family (such as Fas). Fas receptors initiate the extrinsic pathway of apoptosis through a cytoplasmic component known as the death domain. Upon binding Fas ligand (FasL), the receptors trimerize, allowing their death domains to form a binding site for an adapter protein called Fas-associated death domain (FADD). Receptor-bound FADD then stimulates the activation of initiator caspases (8 & 10) that begin an activation cascade culminating in the activation of executioner caspases (3 & 6). These initiate the terminal processes of apoptosis, including cleavage of DNA, fragmentation of the nucleus, organelle autodigestion, and plasma membrane blebbing.

The Fas receptor is expressed on T-lymphocytes and plays an important role in the pathogenesis of numerous diseases, including cancer and autoimmune disorders. Once activated, T lymphocytes begin to express FasL, which can bind to Fas on the same cell or adjacent lymphocytes. During initial clonal expansion, activated T lymphocytes are resistant to Fas-induced apoptosis. However, they become more sensitive with progressive stimulation. In the constant presence of stimulating self-antigens, activated T lymphocytes eventually undergo apoptosis in a process known as activation-induced cell death. Mutations involving Fas or FasL impair this process, resulting in excessive accumulation of autoreactive T-cells and the development of autoimmune diseases such as systemic lupus erythematosus (which this patient appears to have).

(Choice B) As B lymphocytes undergo affinity maturation, cells that exhibit a stronger affinity for the antigen (which acts as a limited growth resource) are able to proliferate more than cells with lower affinity. This results in cells that are more efficient and accurate in binding to pathogens. Affinity maturation does not involve the Fas pathway.

(Choice C) Anergy is a state of prolonged unresponsiveness that occurs in T lymphocytes as a form of immune tolerance. It occurs when self-reactive T cells bind MHC molecules without receiving the necessary costimulatory signal (ie, binding of CD28 on T cells with the B7 on antigen-presenting cells).

(Choice D) Isotype switching is the process through which activated B lymphocytes switch production from IgM immunoglobulins to IgG and IgA isotypes. This process requires the interaction of CD40 on activated B cells with CD40 ligand expressed by activated T cells and is modulated by cytokines secreted by T cells.

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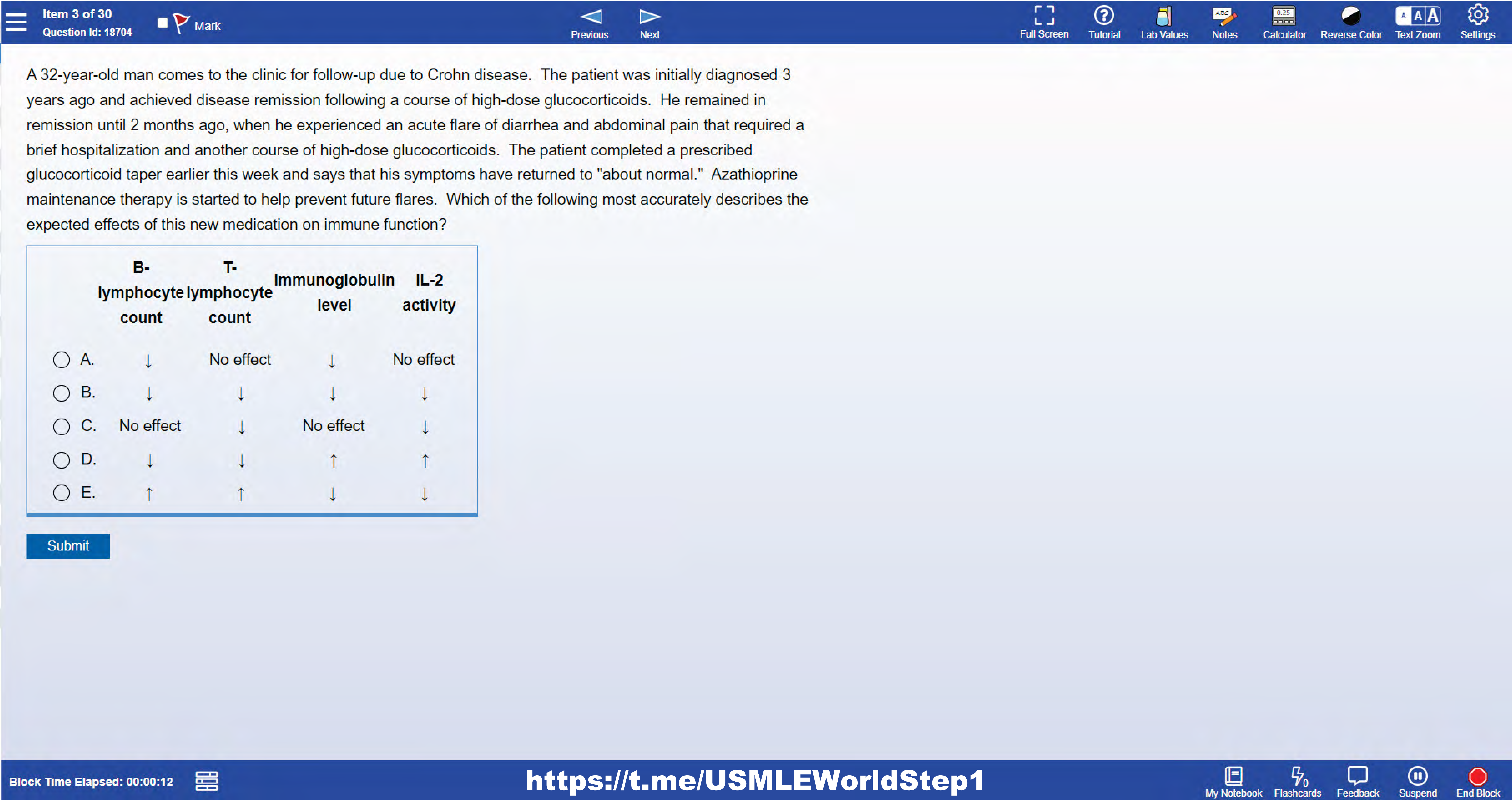
(Choice E) On exposure to an antigen, naïve T helper (T_H0) cells differentiate into T_H1 (cell-mediating) and T_H2 (antibody-mediating) subtypes based on the local cytokine milieu. IFN-γ and IL-12 induce T_H1 formation; IL-4 stimulates T_H2 development.

Educational objective:

The Fas receptor acts to initiate the extrinsic pathway of apoptosis. Mutations involving the Fas receptor or Fas ligand can prevent apoptosis of autoreactive lymphocytes, thereby increasing the risk of autoimmune disorders such as systemic lupus erythematosus.

References

- Activation-induced cell death in T cells.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A 32-year-old man comes to the clinic for follow-up due to Crohn disease. The patient was initially diagnosed 3 years ago and achieved disease remission following a course of high-dose glucocorticoids. He remained in remission until 2 months ago, when he experienced an acute flare of diarrhea and abdominal pain that required a brief hospitalization and another course of high-dose glucocorticoids. The patient completed a prescribed glucocorticoid taper earlier this week and says that his symptoms have returned to "about normal." Azathioprine maintenance therapy is started to help prevent future flares. Which of the following most accurately describes the expected effects of this new medication on immune function?

	B-lymphocyte count	**T-lymphocyte count**	**Immunoglobulin level**	**IL-2 activity**
○ A.	↓	No effect	↓	No effect
○ B.	↓	↓	↓	↓
○ C.	No effect	↓	No effect	↓
○ D.	↓	↓	↑	↑
○ E.	↑	↑	↓	↓

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		B-lymphocyte count	T-lymphocyte count	Immunoglobulin level	IL-2 activity	
✗	● A.	↓	No effect	↓	No effect	(7%)
✓	○ B.	↓	↓	↓	↓	(69%)
	○ C.	No effect	↓	No effect	↓	(20%)
	○ D.	↓	↓	↑	↑	(2%)
	○ E.	↑	↑	↓	↓	(0%)

Incorrect
Correct answer
B

69%
Answered correctly

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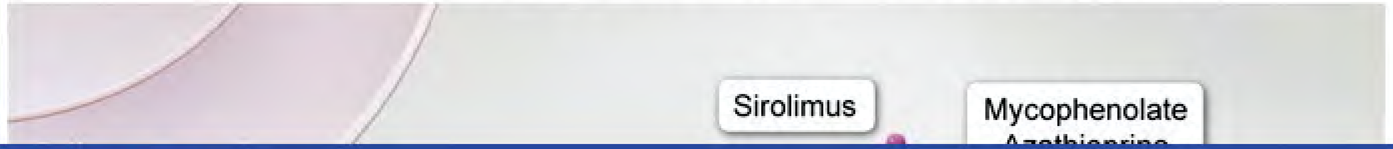
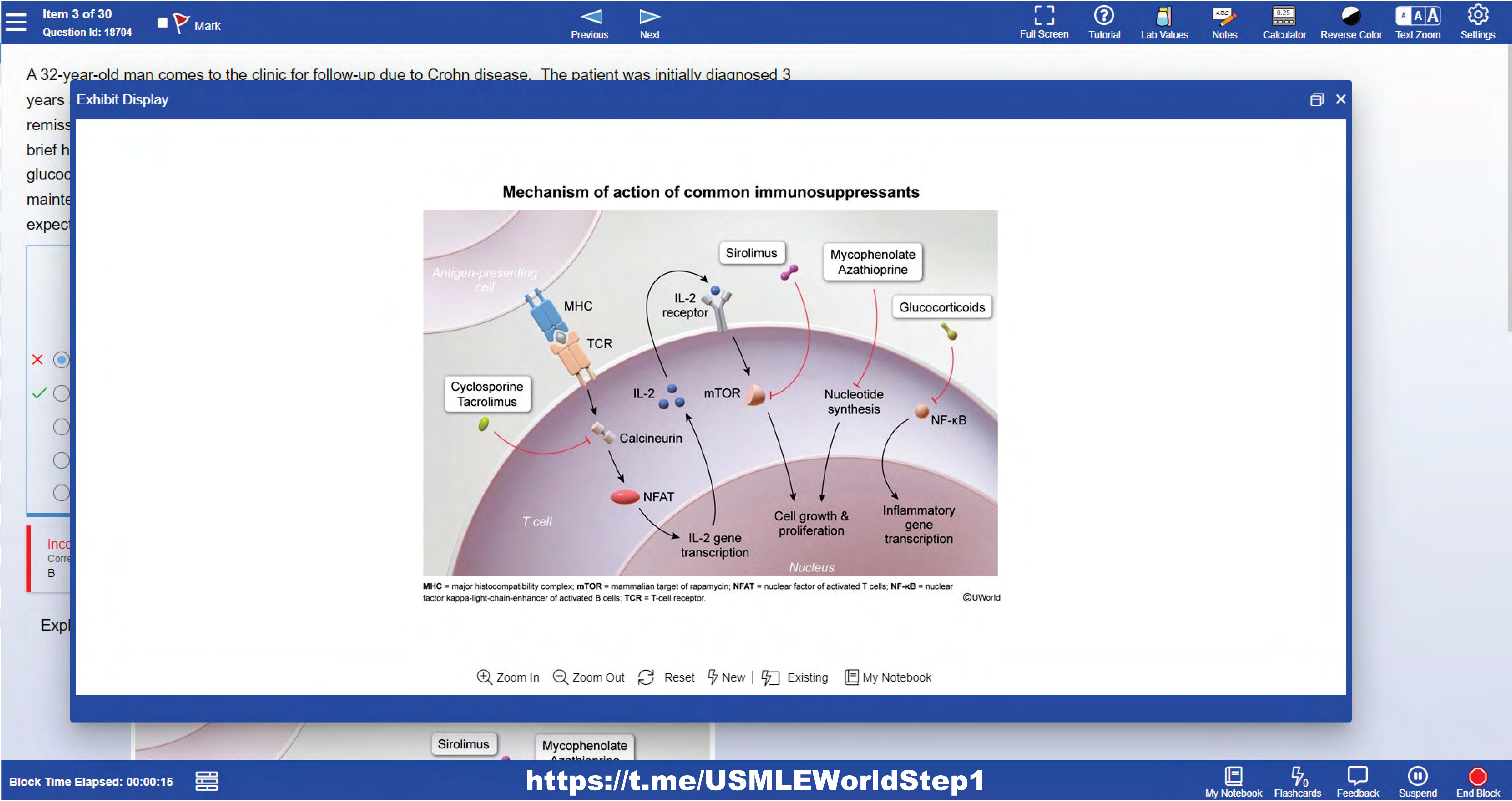
Version

Explanation

Mechanism of action of common immunosuppressants

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Mechanism of action of common immunosuppressants

Antigen-presenting cell
MHC
TCR
Sirolimus
IL-2 receptor
Mycophenolate
Azathioprine
Glucocorticoids
Cyclosporine
Tacrolimus
IL-2
mTOR
Nucleotide synthesis
NF-κB
Calcineurin
NFAT
T cell
IL-2 gene transcription
Cell growth & proliferation
Inflammatory gene transcription
Nucleus

MHC = major histocompatibility complex; **mTOR** = mammalian target of rapamycin; **NFAT** = nuclear factor of activated T cells; **NF-κB** = nuclear factor kappa-light-chain-enhancer of activated B cells; **TCR** = T-cell receptor.

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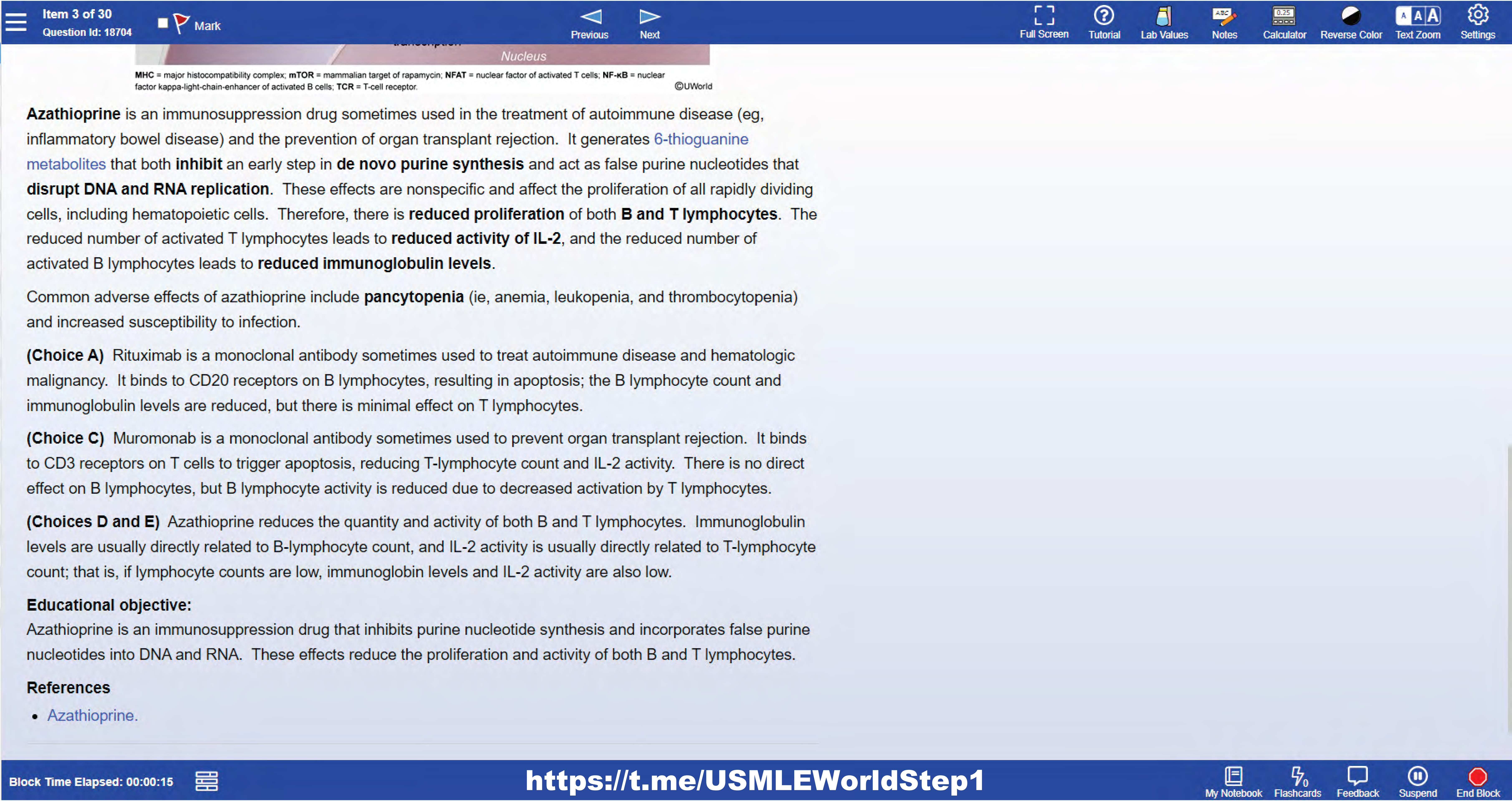

MHC = major histocompatibility complex; **mTOR** = mammalian target of rapamycin; **NFAT** = nuclear factor of activated T cells; **NF-κB** = nuclear factor kappa-light-chain-enhancer of activated B cells; **TCR** = T-cell receptor.

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Azathioprine is an immunosuppression drug sometimes used in the treatment of autoimmune disease (eg, inflammatory bowel disease) and the prevention of organ transplant rejection. It generates 6-thioguanine metabolites that both **inhibit** an early step in **de novo purine synthesis** and act as false purine nucleotides that **disrupt DNA and RNA replication**. These effects are nonspecific and affect the proliferation of all rapidly dividing cells, including hematopoietic cells. Therefore, there is **reduced proliferation** of both **B and T lymphocytes**. The reduced number of activated T lymphocytes leads to **reduced activity of IL-2**, and the reduced number of activated B lymphocytes leads to **reduced immunoglobulin levels**.

Common adverse effects of azathioprine include **pancytopenia** (ie, anemia, leukopenia, and thrombocytopenia) and increased susceptibility to infection.

(Choice A) Rituximab is a monoclonal antibody sometimes used to treat autoimmune disease and hematologic malignancy. It binds to CD20 receptors on B lymphocytes, resulting in apoptosis; the B lymphocyte count and immunoglobulin levels are reduced, but there is minimal effect on T lymphocytes.

(Choice C) Muromonab is a monoclonal antibody sometimes used to prevent organ transplant rejection. It binds to CD3 receptors on T cells to trigger apoptosis, reducing T-lymphocyte count and IL-2 activity. There is no direct effect on B lymphocytes, but B lymphocyte activity is reduced due to decreased activation by T lymphocytes.

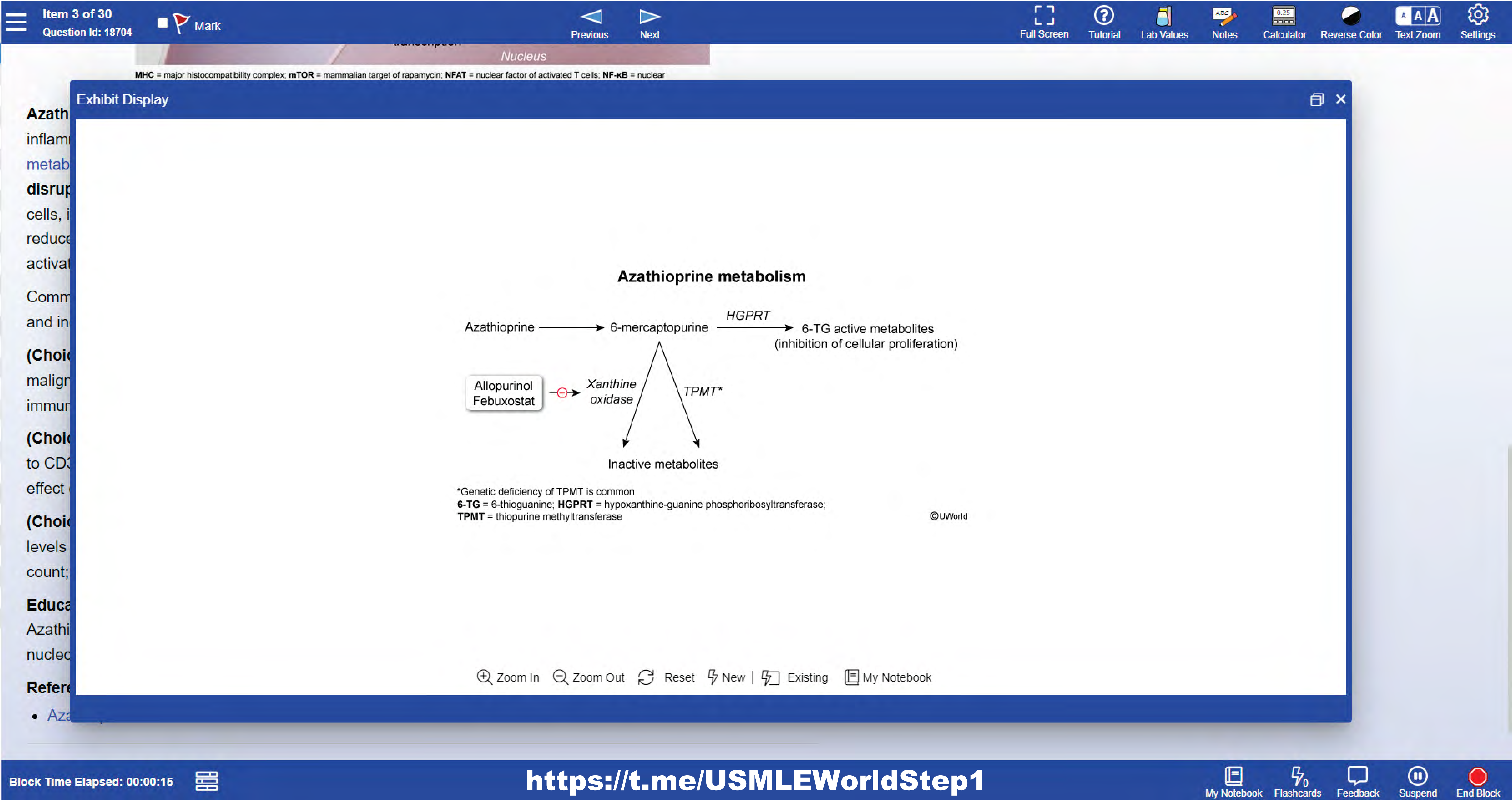
(Choices D and E) Azathioprine reduces the quantity and activity of both B and T lymphocytes. Immunoglobulin levels are usually directly related to B-lymphocyte count, and IL-2 activity is usually directly related to T-lymphocyte count; that is, if lymphocyte counts are low, immunoglobin levels and IL-2 activity are also low.

Educational objective:

Azathioprine is an immunosuppression drug that inhibits purine nucleotide synthesis and incorporates false purine nucleotides into DNA and RNA. These effects reduce the proliferation and activity of both B and T lymphocytes.

References

- Azathioprine.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Nucleus
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Azathioprine
6-mercaptopurine
HGPRT
6-TG active metabolites
(inhibition of cellular proliferation)
Allopurinol
Febuxostat
Xanthine oxidase
TPMT*
Inactive metabolites
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MHC = major histocompatibility complex; **mTOR** = mammalian target of rapamycin; **NFAT** = nuclear factor of activated T cells; **NF-κB** = nuclear

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Azathioprine metabolism

*Genetic deficiency of TPMT is common
6-TG = 6-thioguanine; **HGPRT** = hypoxanthine-guanine phosphoribosyltransferase;
TPMT = thiopurine methyltransferase

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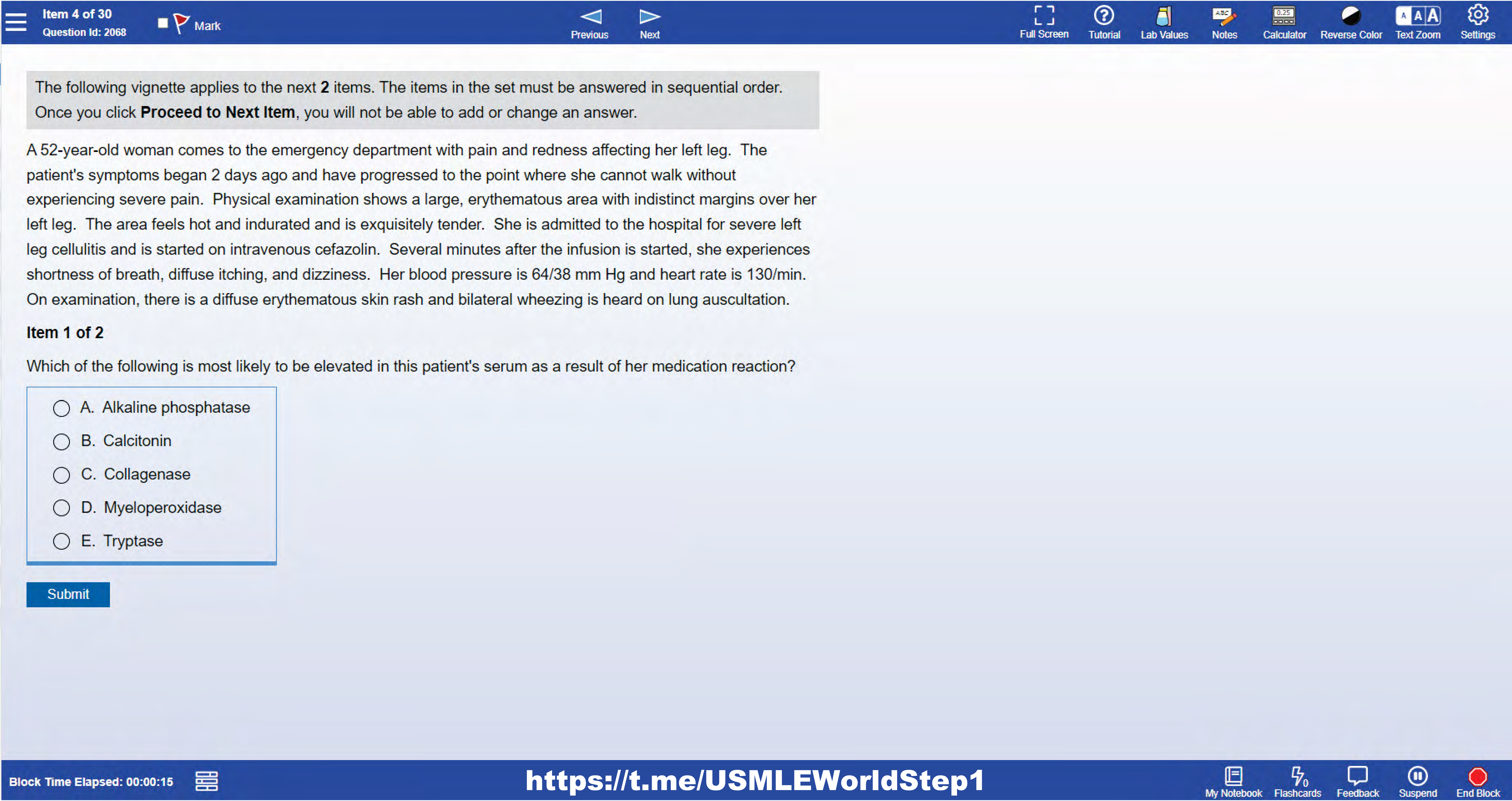
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The following vignette applies to the next **2** items. The items in the set must be answered in sequential order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 52-year-old woman comes to the emergency department with pain and redness affecting her left leg. The patient's symptoms began 2 days ago and have progressed to the point where she cannot walk without experiencing severe pain. Physical examination shows a large, erythematous area with indistinct margins over her left leg. The area feels hot and indurated and is exquisitely tender. She is admitted to the hospital for severe left leg cellulitis and is started on intravenous cefazolin. Several minutes after the infusion is started, she experiences shortness of breath, diffuse itching, and dizziness. Her blood pressure is 64/38 mm Hg and heart rate is 130/min. On examination, there is a diffuse erythematous skin rash and bilateral wheezing is heard on lung auscultation.

Item 1 of 2

Which of the following is most likely to be elevated in this patient's serum as a result of her medication reaction?

○ A. Alkaline phosphatase
○ B. Calcitonin
○ C. Collagenase
○ D. Myeloperoxidase
○ E. Tryptase

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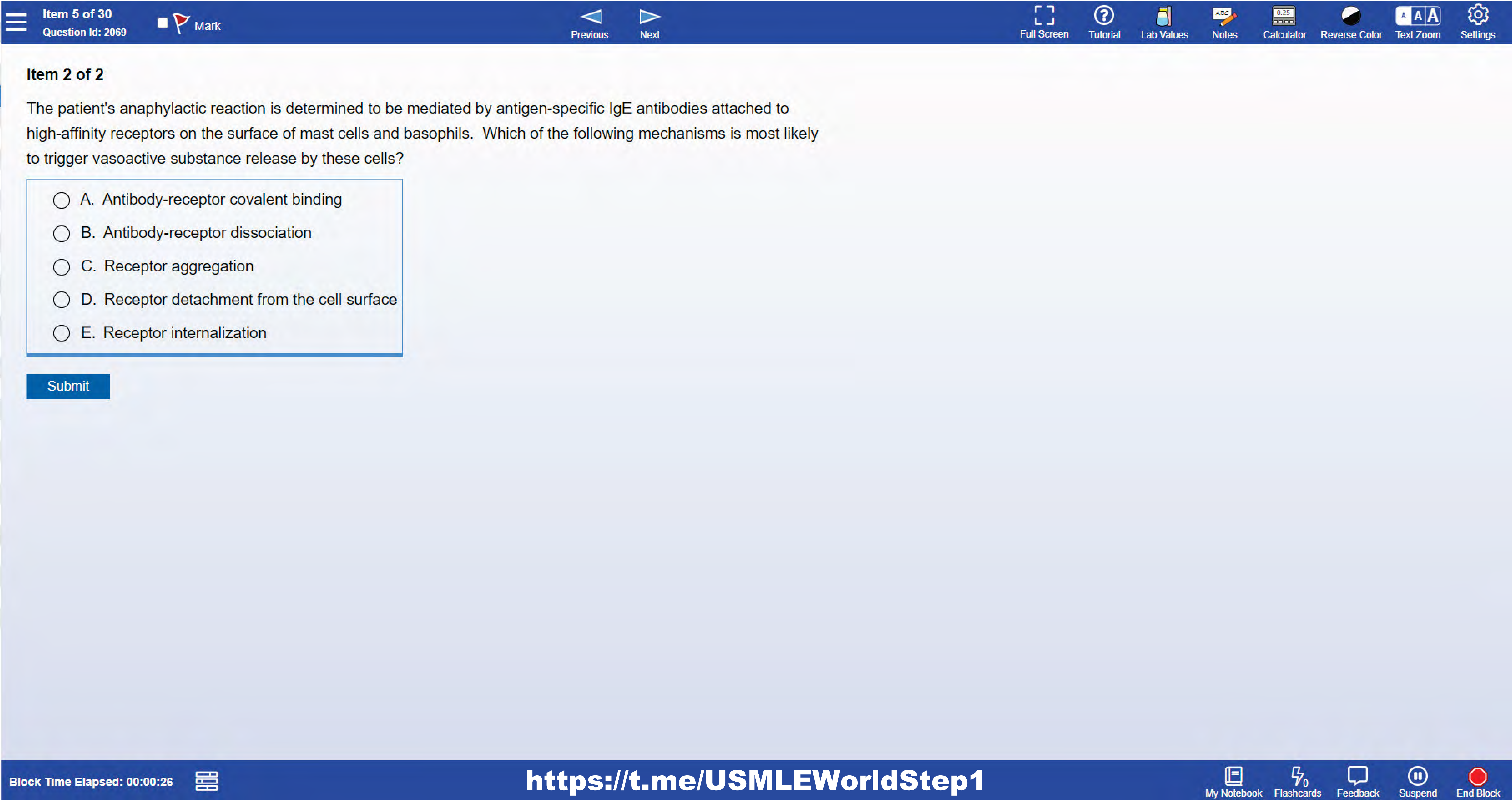
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Item 5 of 30
Question Id: 2069

Item 2 of 2

The patient's anaphylactic reaction is determined to be mediated by antigen-specific IgE antibodies attached to high-affinity receptors on the surface of mast cells and basophils. Which of the following mechanisms is most likely to trigger vasoactive substance release by these cells?

- ○ A. Antibody-receptor covalent binding
- ○ B. Antibody-receptor dissociation
- ○ C. Receptor aggregation
- ○ D. Receptor detachment from the cell surface
- ○ E. Receptor internalization

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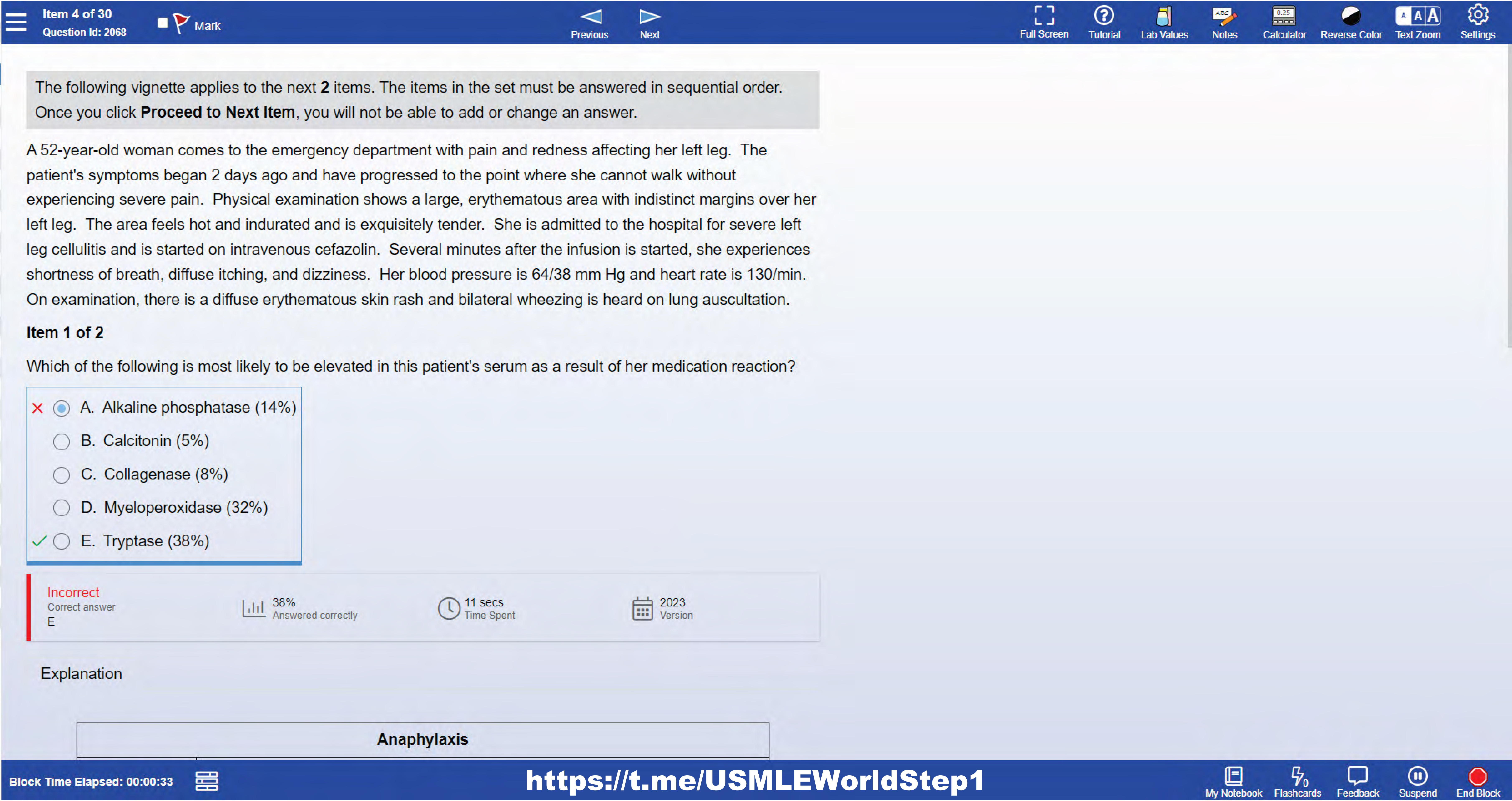
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Item 1 of 2

Which of the following is most likely to be elevated in this patient's serum as a result of her medication reaction?

✗ ● A. Alkaline phosphatase (14%)
○ B. Calcitonin (5%)
○ C. Collagenase (8%)
○ D. Myeloperoxidase (32%)
✓ ○ E. Tryptase (38%)

Incorrect
Correct answer
E

38%
Answered correctly

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Explanation

Anaphylaxis

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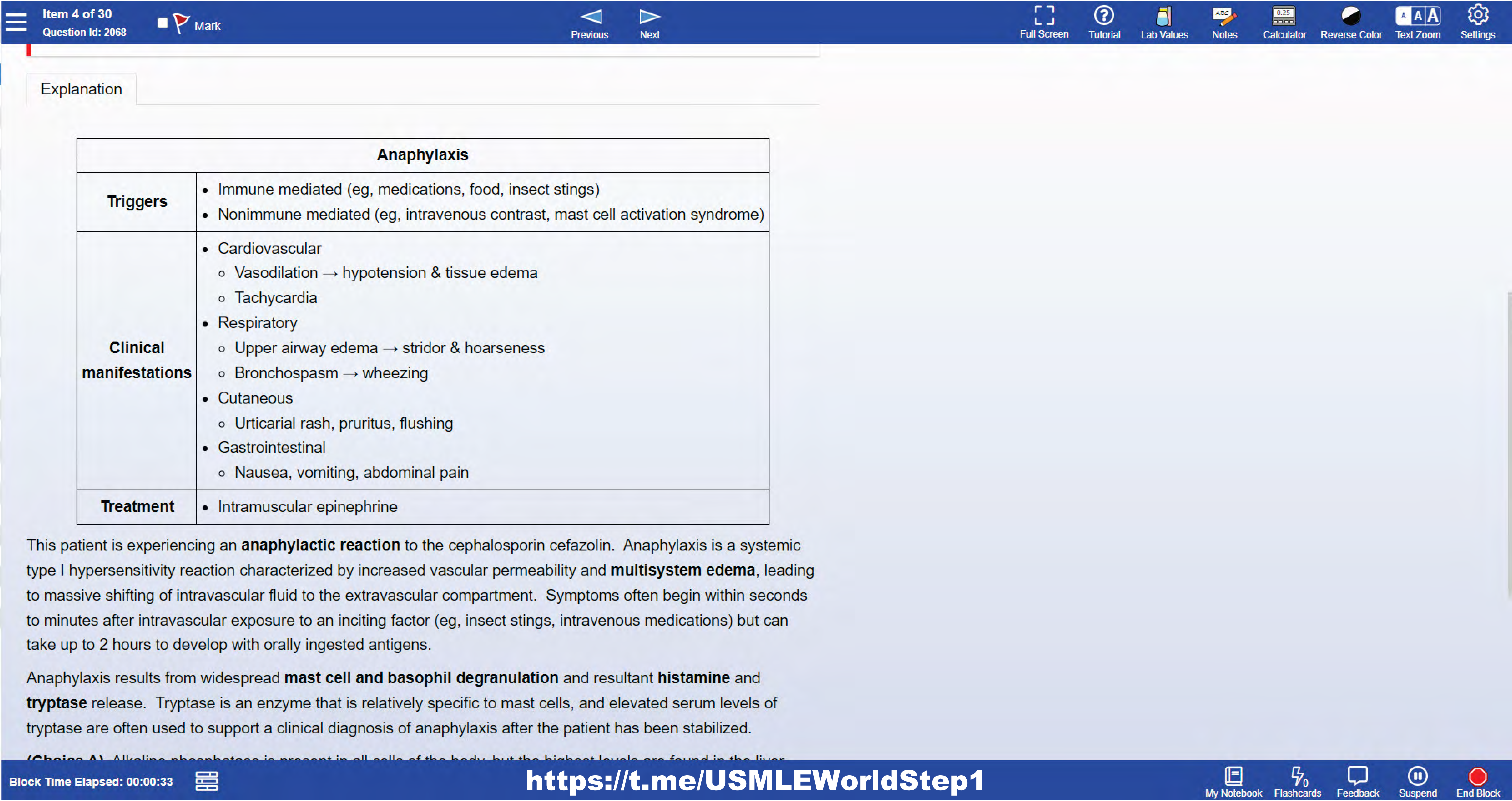
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Explanation

Anaphylaxis	
Triggers	- Immune mediated (eg, medications, food, insect stings) - Nonimmune mediated (eg, intravenous contrast, mast cell activation syndrome)

Clinical manifestations	- Cardiovascular
	  ○ Vasodilation → hypotension & tissue edema
	  ○ Tachycardia
	- Respiratory
	  ○ Upper airway edema → stridor & hoarseness
	  ○ Bronchospasm → wheezing
	- Cutaneous
	  ○ Urticarial rash, pruritus, flushing
	- Gastrointestinal
	  ○ Nausea, vomiting, abdominal pain

Treatment	- Intramuscular epinephrine

This patient is experiencing an **anaphylactic reaction** to the cephalosporin cefazolin. Anaphylaxis is a systemic type I hypersensitivity reaction characterized by increased vascular permeability and **multisystem edema**, leading to massive shifting of intravascular fluid to the extravascular compartment. Symptoms often begin within seconds to minutes after intravascular exposure to an inciting factor (eg, insect stings, intravenous medications) but can take up to 2 hours to develop with orally ingested antigens.

Anaphylaxis results from widespread **mast cell and basophil degranulation** and resultant **histamine** and **tryptase** release. Tryptase is an enzyme that is relatively specific to mast cells, and elevated serum levels of tryptase are often used to support a clinical diagnosis of anaphylaxis after the patient has been stabilized.

(Choice A) Alkaline phosphatase is present in all cells of the body, but the highest levels are found in the liver

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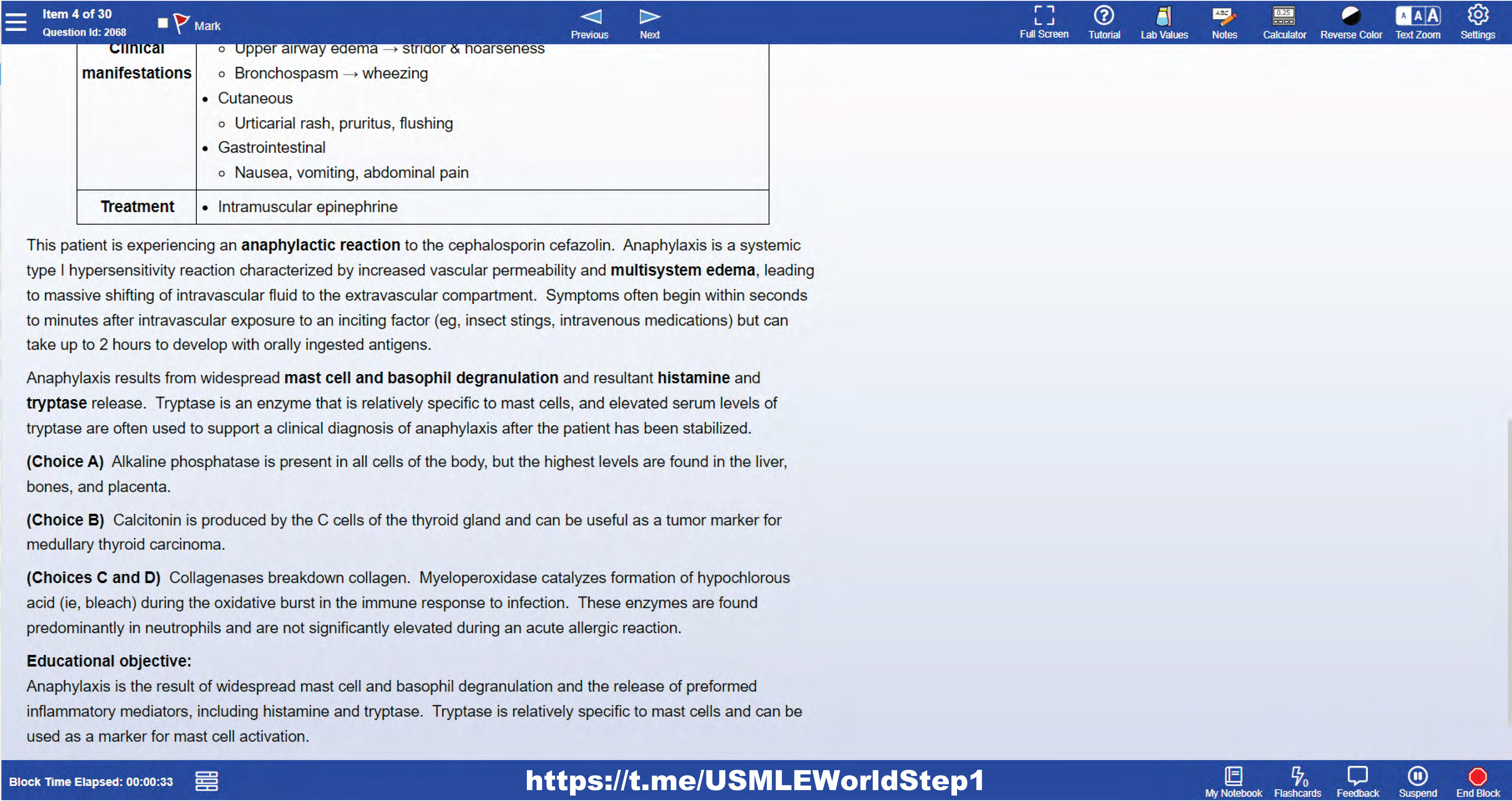

Clinical manifestations	◦ Upper airway edema → stridor & hoarseness ◦ Bronchospasm → wheezing • Cutaneous ◦ Urticarial rash, pruritus, flushing • Gastrointestinal ◦ Nausea, vomiting, abdominal pain
Treatment	• Intramuscular epinephrine

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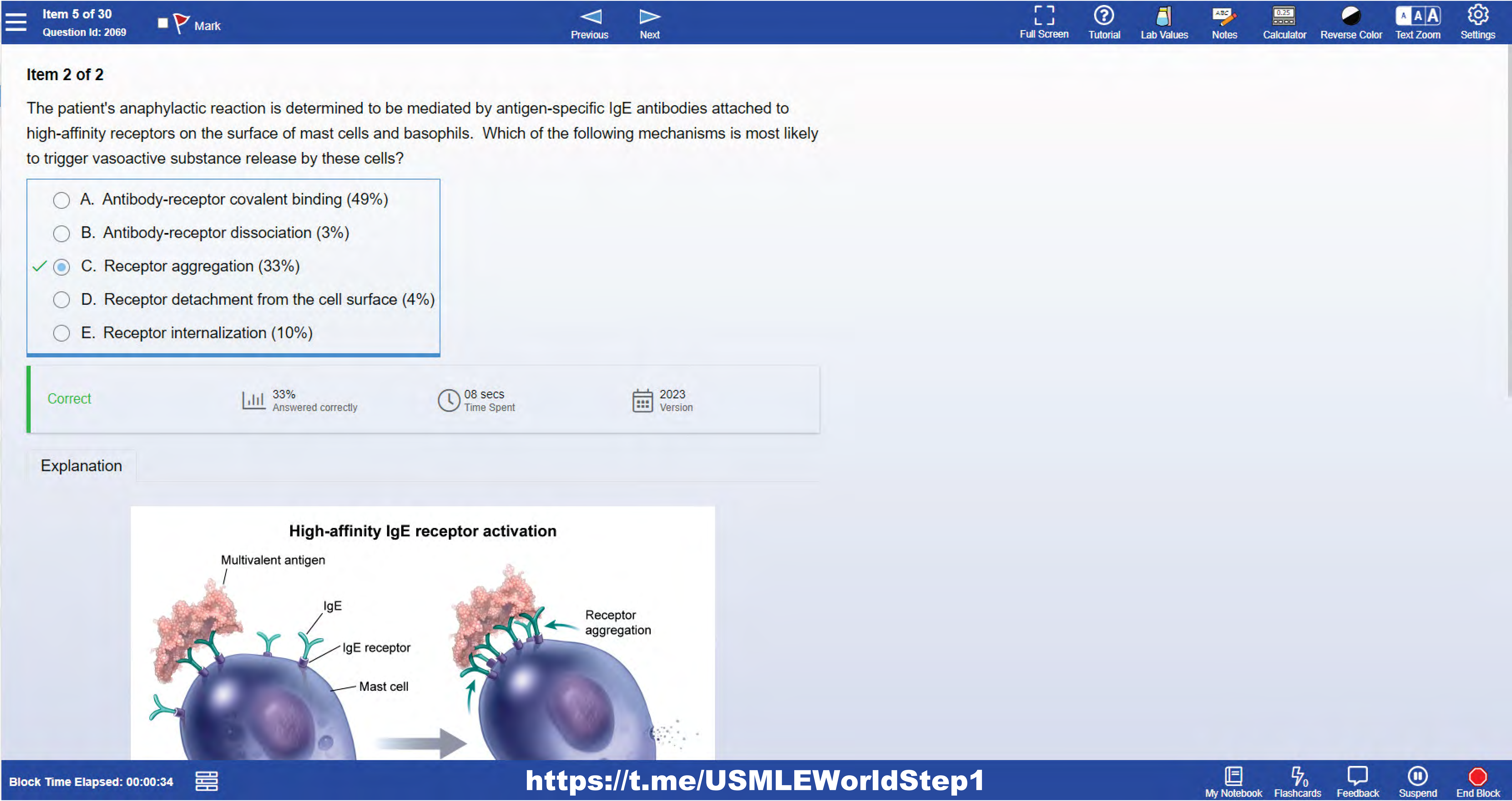
(Choice A) Alkaline phosphatase is present in all cells of the body, but the highest levels are found in the liver, bones, and placenta.

(Choice B) Calcitonin is produced by the C cells of the thyroid gland and can be useful as a tumor marker for medullary thyroid carcinoma.

(Choices C and D) Collagenases breakdown collagen. Myeloperoxidase catalyzes formation of hypochlorous acid (ie, bleach) during the oxidative burst in the immune response to infection. These enzymes are found predominantly in neutrophils and are not significantly elevated during an acute allergic reaction.

Educational objective:
Anaphylaxis is the result of widespread mast cell and basophil degranulation and the release of preformed inflammatory mediators, including histamine and tryptase. Tryptase is relatively specific to mast cells and can be used as a marker for mast cell activation.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The patient's anaphylactic reaction is determined to be mediated by antigen-specific IgE antibodies attached to high-affinity receptors on the surface of mast cells and basophils. Which of the following mechanisms is most likely to trigger vasoactive substance release by these cells?

- ○ A. Antibody-receptor covalent binding (49%)
- ○ B. Antibody-receptor dissociation (3%)
- ✓ ● C. Receptor aggregation (33%)
- ○ D. Receptor detachment from the cell surface (4%)
- ○ E. Receptor internalization (10%)

Correct

33% Answered correctly

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Explanation

High-affinity IgE receptor activation

Multivalent antigen
IgE
IgE receptor
Mast cell
Receptor aggregation
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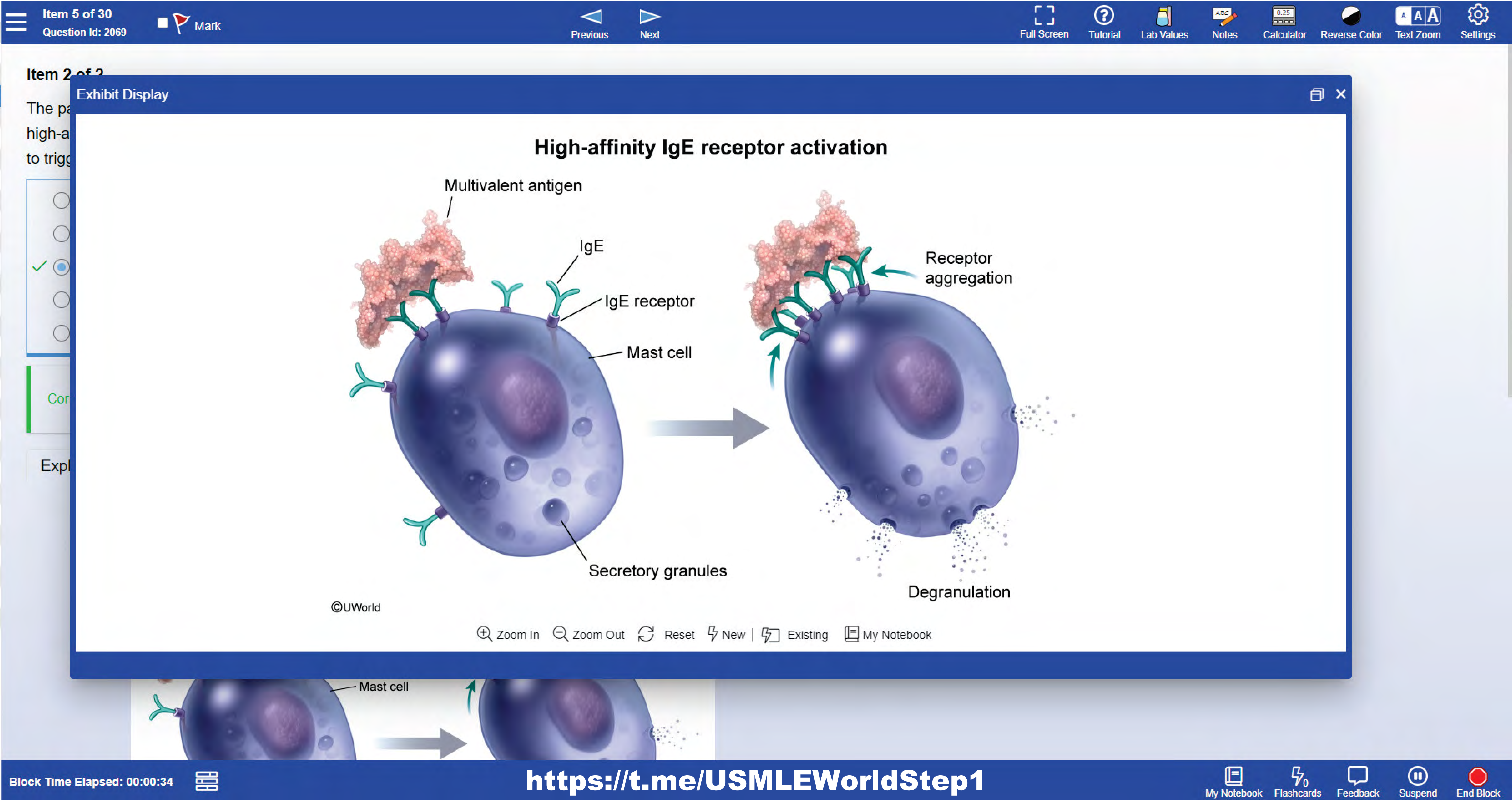
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High-affinity IgE receptor activation

Multivalent antigen
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Receptor aggregation
Degranulation
Mast cell

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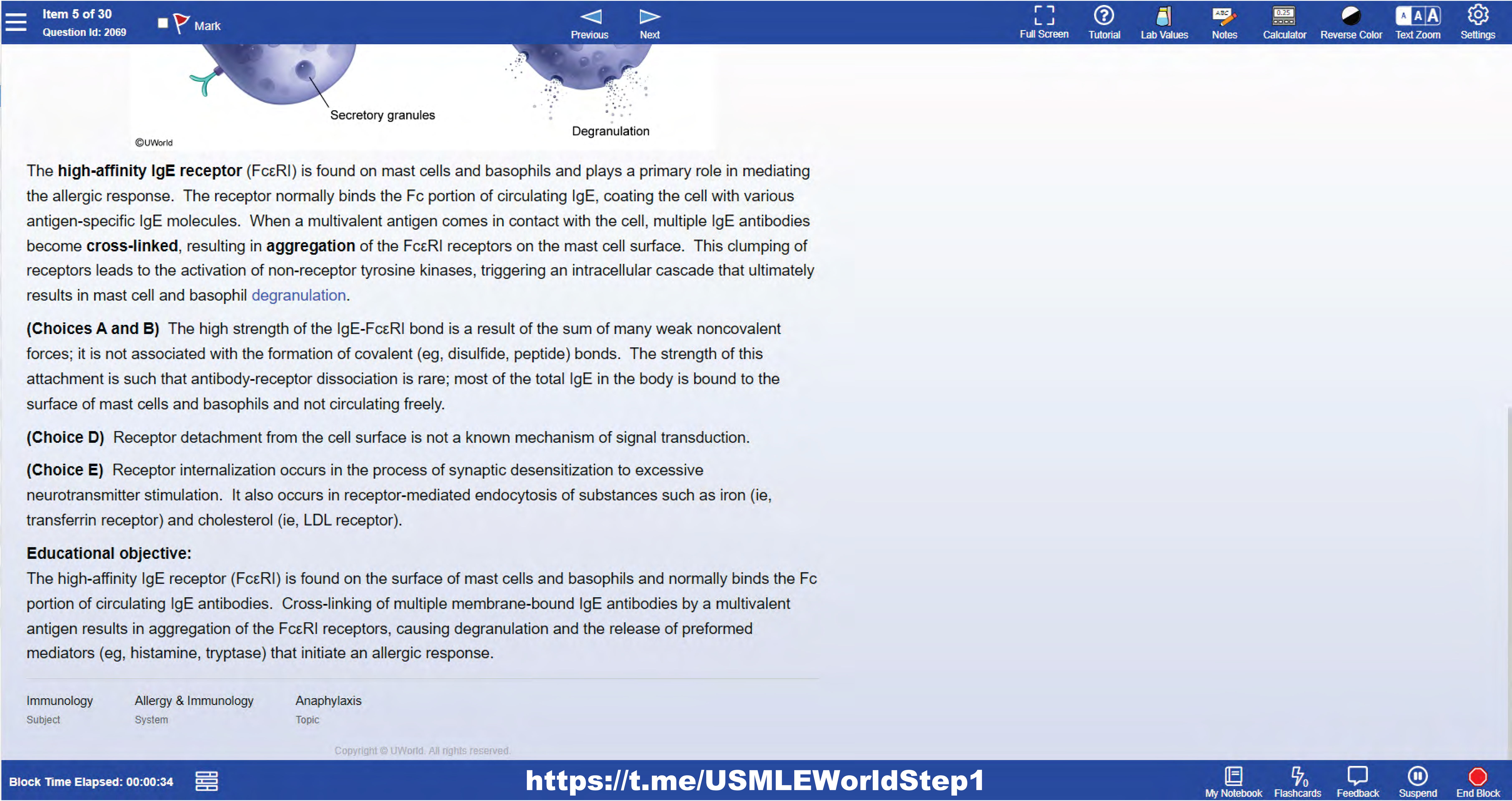
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The **high-affinity IgE receptor** (FcεRI) is found on mast cells and basophils and plays a primary role in mediating the allergic response. The receptor normally binds the Fc portion of circulating IgE, coating the cell with various antigen-specific IgE molecules. When a multivalent antigen comes in contact with the cell, multiple IgE antibodies become **cross-linked**, resulting in **aggregation** of the FcεRI receptors on the mast cell surface. This clumping of receptors leads to the activation of non-receptor tyrosine kinases, triggering an intracellular cascade that ultimately results in mast cell and basophil degranulation.

(Choices A and B) The high strength of the IgE-FcεRI bond is a result of the sum of many weak noncovalent forces; it is not associated with the formation of covalent (eg, disulfide, peptide) bonds. The strength of this attachment is such that antibody-receptor dissociation is rare; most of the total IgE in the body is bound to the surface of mast cells and basophils and not circulating freely.

(Choice D) Receptor detachment from the cell surface is not a known mechanism of signal transduction.

(Choice E) Receptor internalization occurs in the process of synaptic desensitization to excessive neurotransmitter stimulation. It also occurs in receptor-mediated endocytosis of substances such as iron (ie, transferrin receptor) and cholesterol (ie, LDL receptor).

Educational objective:

The high-affinity IgE receptor (FcεRI) is found on the surface of mast cells and basophils and normally binds the Fc portion of circulating IgE antibodies. Cross-linking of multiple membrane-bound IgE antibodies by a multivalent antigen results in aggregation of the FcεRI receptors, causing degranulation and the release of preformed mediators (eg, histamine, tryptase) that initiate an allergic response.

Immunology	Allergy & Immunology	Anaphylaxis
Subject	System	Topic

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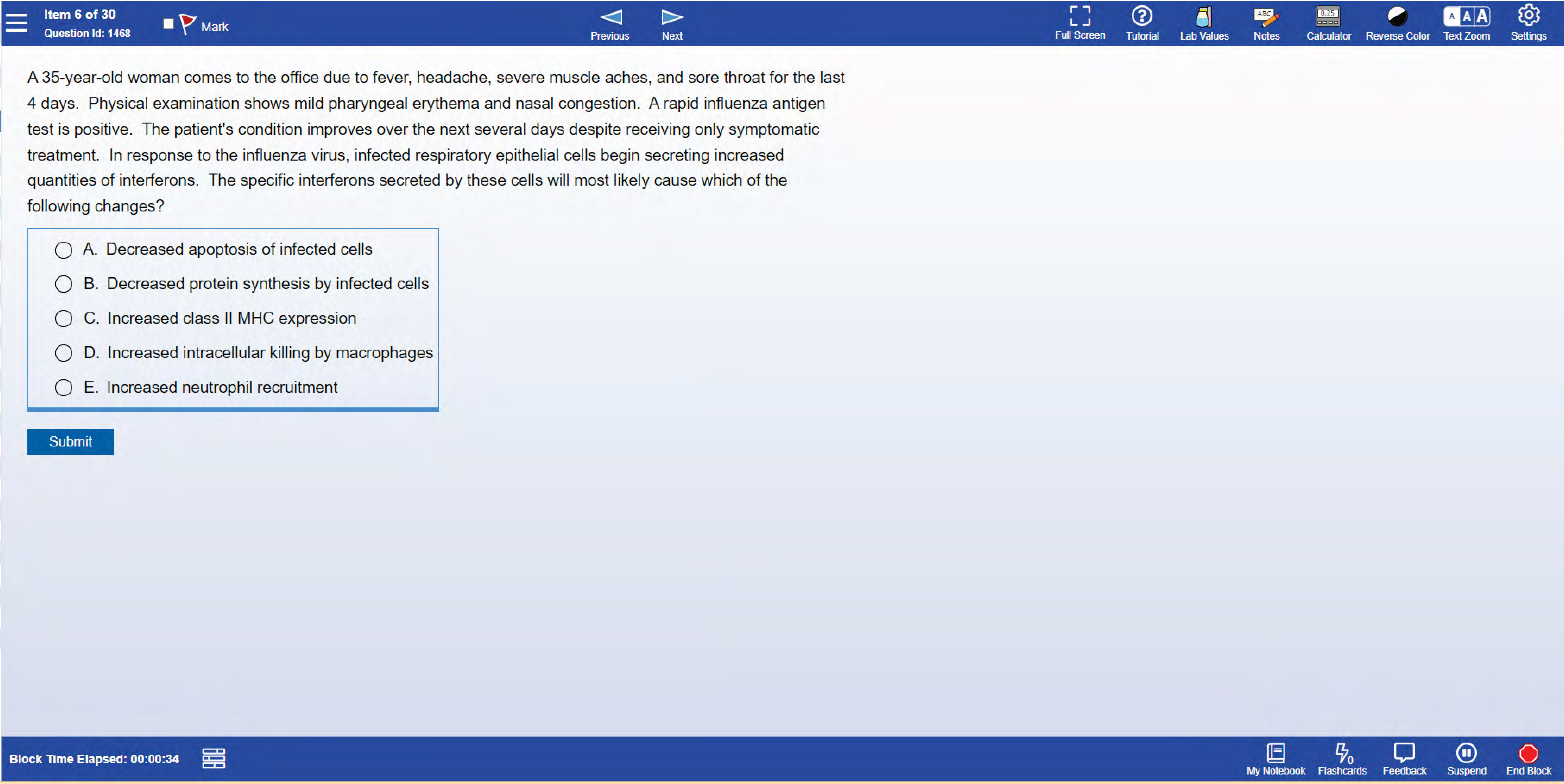
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A 35-year-old woman comes to the office due to fever, headache, severe muscle aches, and sore throat for the last 4 days. Physical examination shows mild pharyngeal erythema and nasal congestion. A rapid influenza antigen test is positive. The patient's condition improves over the next several days despite receiving only symptomatic treatment. In response to the influenza virus, infected respiratory epithelial cells begin secreting increased quantities of interferons. The specific interferons secreted by these cells will most likely cause which of the following changes?

○ A. Decreased apoptosis of infected cells
○ B. Decreased protein synthesis by infected cells
○ C. Increased class II MHC expression
○ D. Increased intracellular killing by macrophages
○ E. Increased neutrophil recruitment

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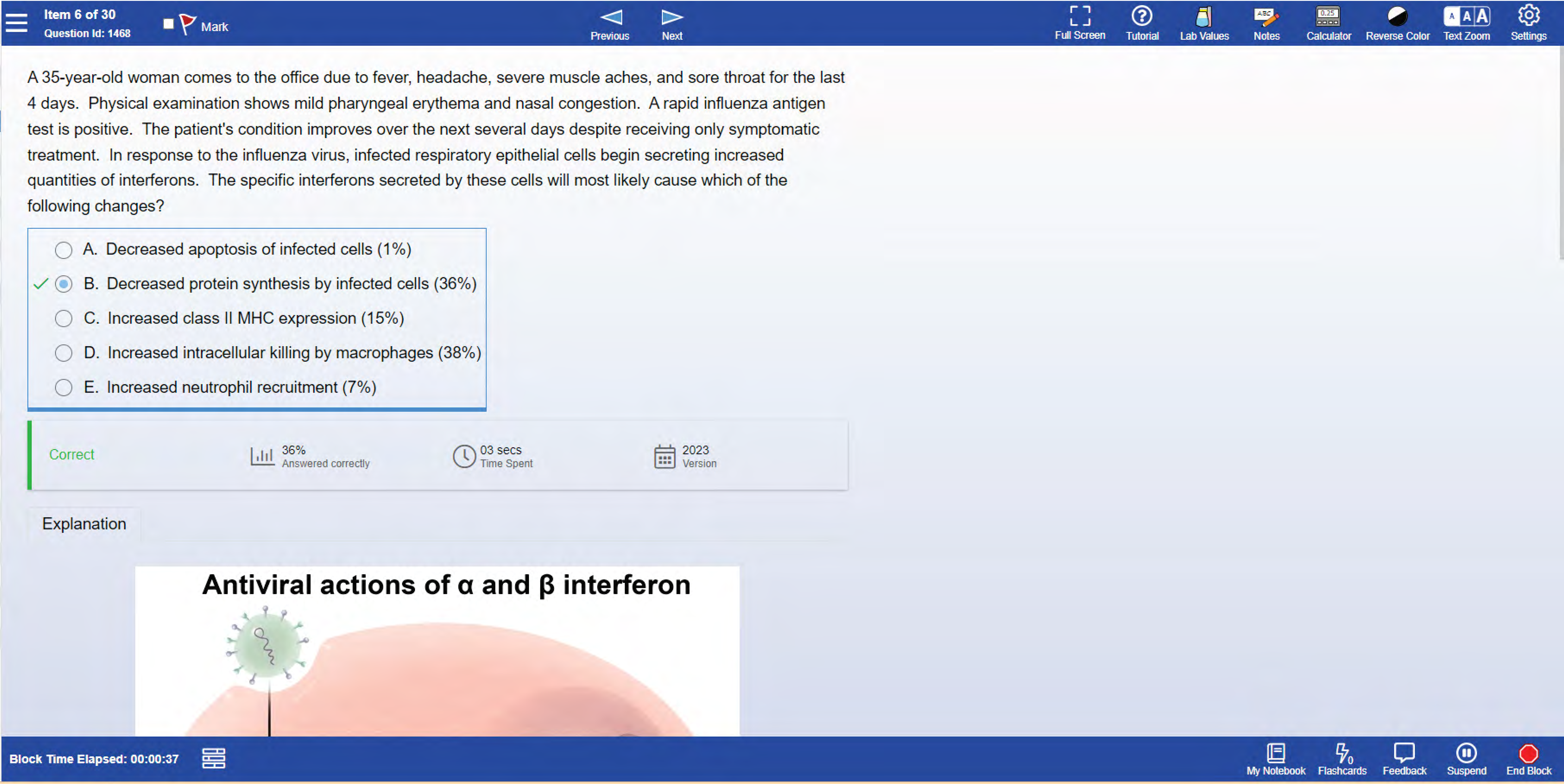
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A 35-year-old woman comes to the office due to fever, headache, severe muscle aches, and sore throat for the last 4 days. Physical examination shows mild pharyngeal erythema and nasal congestion. A rapid influenza antigen test is positive. The patient's condition improves over the next several days despite receiving only symptomatic treatment. In response to the influenza virus, infected respiratory epithelial cells begin secreting increased quantities of interferons. The specific interferons secreted by these cells will most likely cause which of the following changes?

- ○ A. Decreased apoptosis of infected cells (1%)
- ✓ ● B. Decreased protein synthesis by infected cells (36%)
- ○ C. Increased class II MHC expression (15%)
- ○ D. Increased intracellular killing by macrophages (38%)
- ○ E. Increased neutrophil recruitment (7%)

Correct | 36% Answered correctly | 03 secs Time Spent | 2023 Version

Explanation

Antiviral actions of α and β interferon

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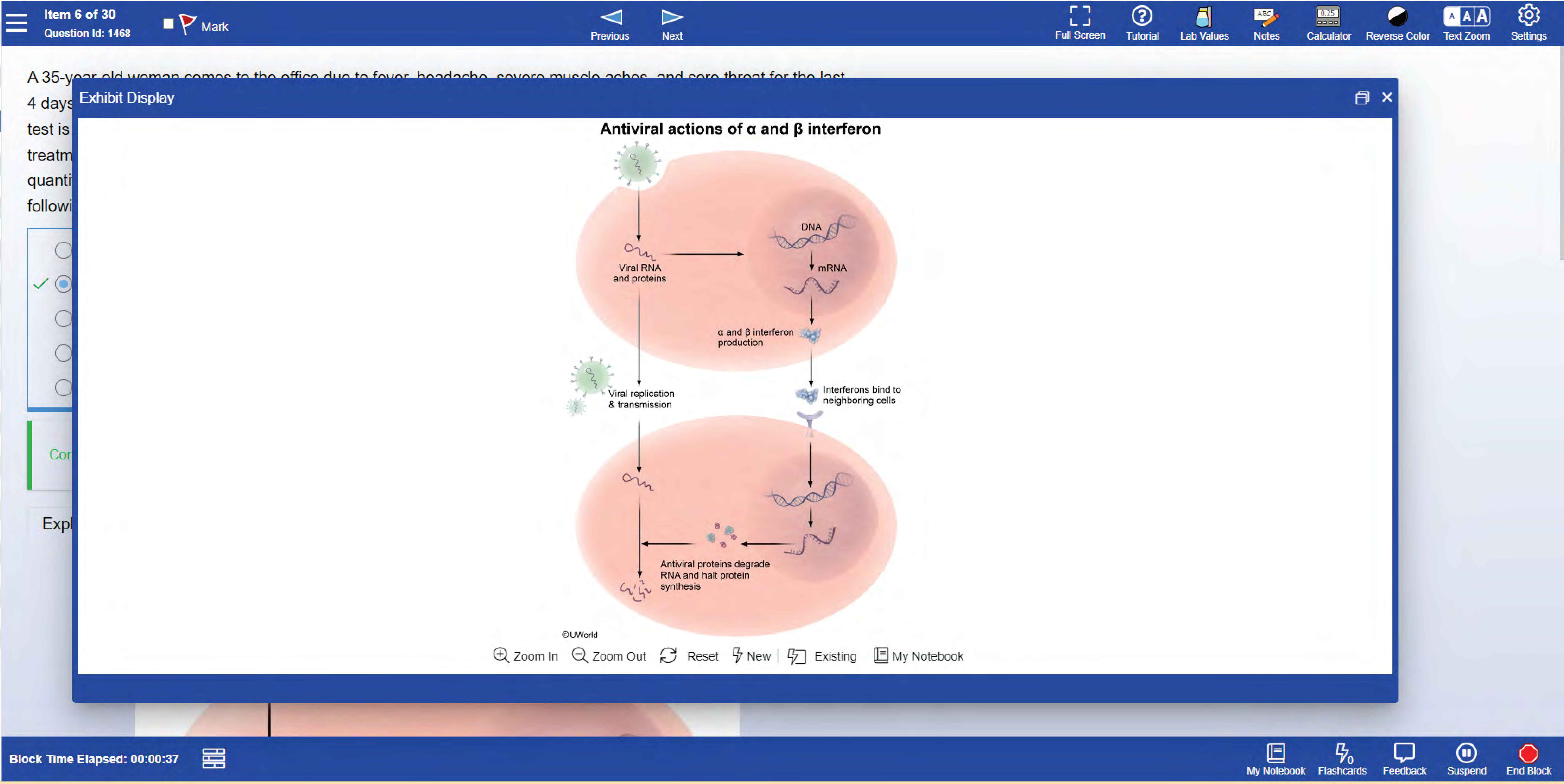
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Antiviral actions of α and β interferon

DNA
mRNA
Viral RNA and proteins
α and β interferon production
Viral replication & transmission
Interferons bind to neighboring cells
Antiviral proteins degrade RNA and halt protein synthesis
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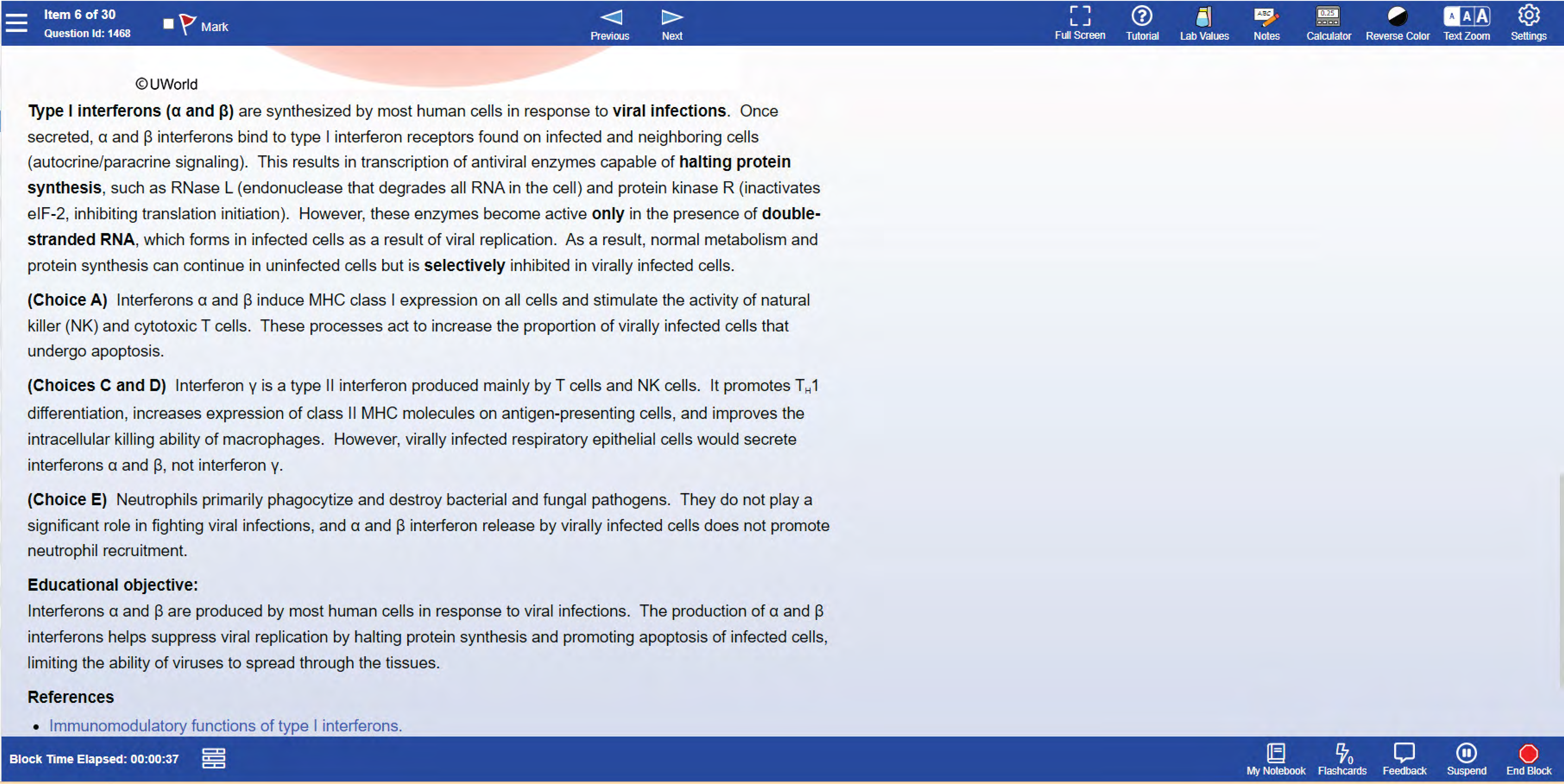

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Type I interferons (α and β) are synthesized by most human cells in response to **viral infections**. Once secreted, α and β interferons bind to type I interferon receptors found on infected and neighboring cells (autocrine/paracrine signaling). This results in transcription of antiviral enzymes capable of **halting protein synthesis**, such as RNase L (endonuclease that degrades all RNA in the cell) and protein kinase R (inactivates eIF-2, inhibiting translation initiation). However, these enzymes become active **only** in the presence of **double-stranded RNA**, which forms in infected cells as a result of viral replication. As a result, normal metabolism and protein synthesis can continue in uninfected cells but is **selectively** inhibited in virally infected cells.

(Choice A) Interferons α and β induce MHC class I expression on all cells and stimulate the activity of natural killer (NK) and cytotoxic T cells. These processes act to increase the proportion of virally infected cells that undergo apoptosis.

(Choices C and D) Interferon γ is a type II interferon produced mainly by T cells and NK cells. It promotes T_H1 differentiation, increases expression of class II MHC molecules on antigen-presenting cells, and improves the intracellular killing ability of macrophages. However, virally infected respiratory epithelial cells would secrete interferons α and β, not interferon γ.

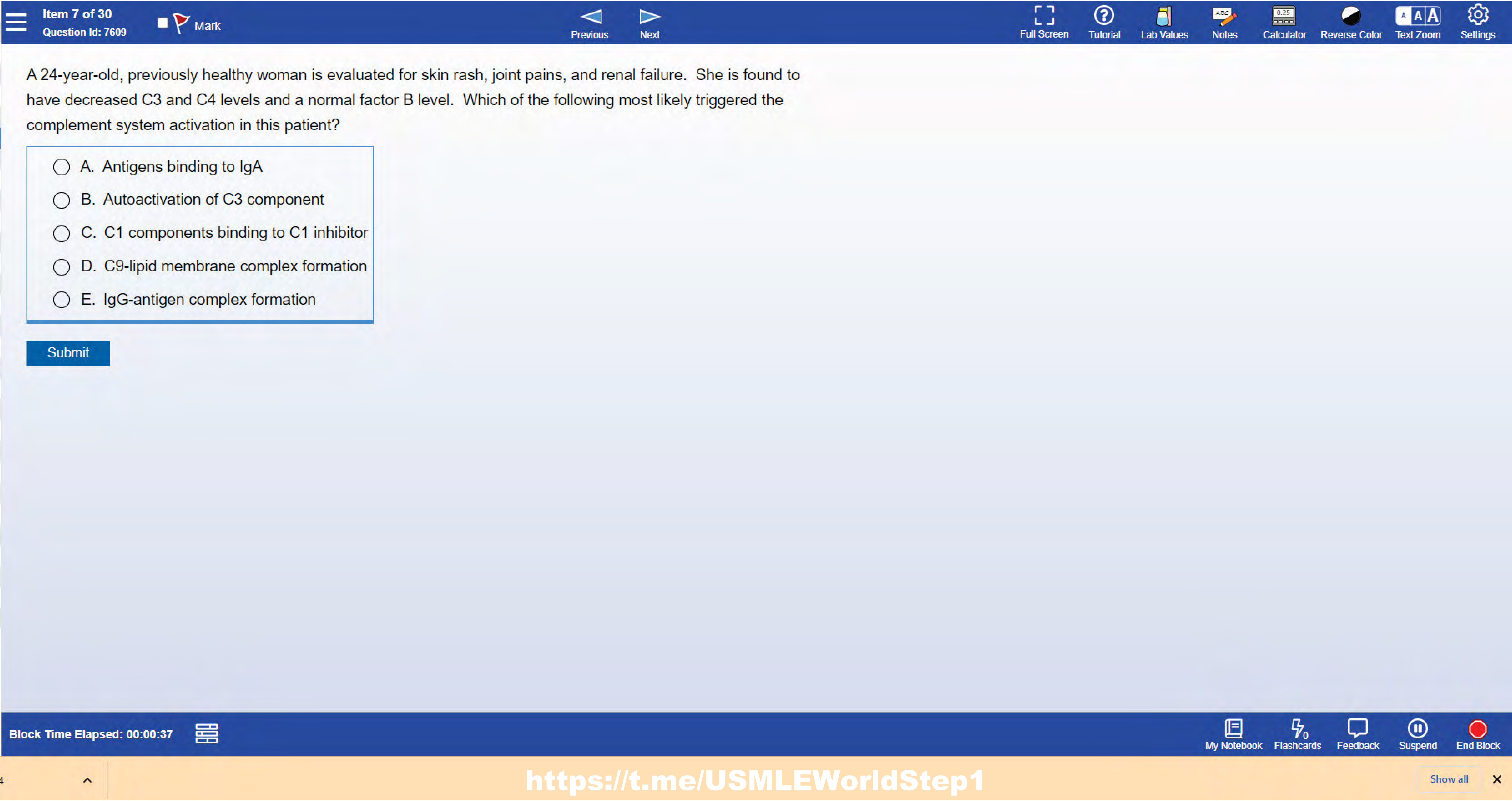
(Choice E) Neutrophils primarily phagocytize and destroy bacterial and fungal pathogens. They do not play a significant role in fighting viral infections, and α and β interferon release by virally infected cells does not promote neutrophil recruitment.

Educational objective:

Interferons α and β are produced by most human cells in response to viral infections. The production of α and β interferons helps suppress viral replication by halting protein synthesis and promoting apoptosis of infected cells, limiting the ability of viruses to spread through the tissues.

References

- Immunomodulatory functions of type I interferons.



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Item 7 of 30
Question Id: 7609

A 24-year-old, previously healthy woman is evaluated for skin rash, joint pains, and renal failure. She is found to have decreased C3 and C4 levels and a normal factor B level. Which of the following most likely triggered the complement system activation in this patient?

○ A. Antigens binding to IgA
○ B. Autoactivation of C3 component
○ C. C1 components binding to C1 inhibitor
○ D. C9-lipid membrane complex formation
○ E. IgG-antigen complex formation

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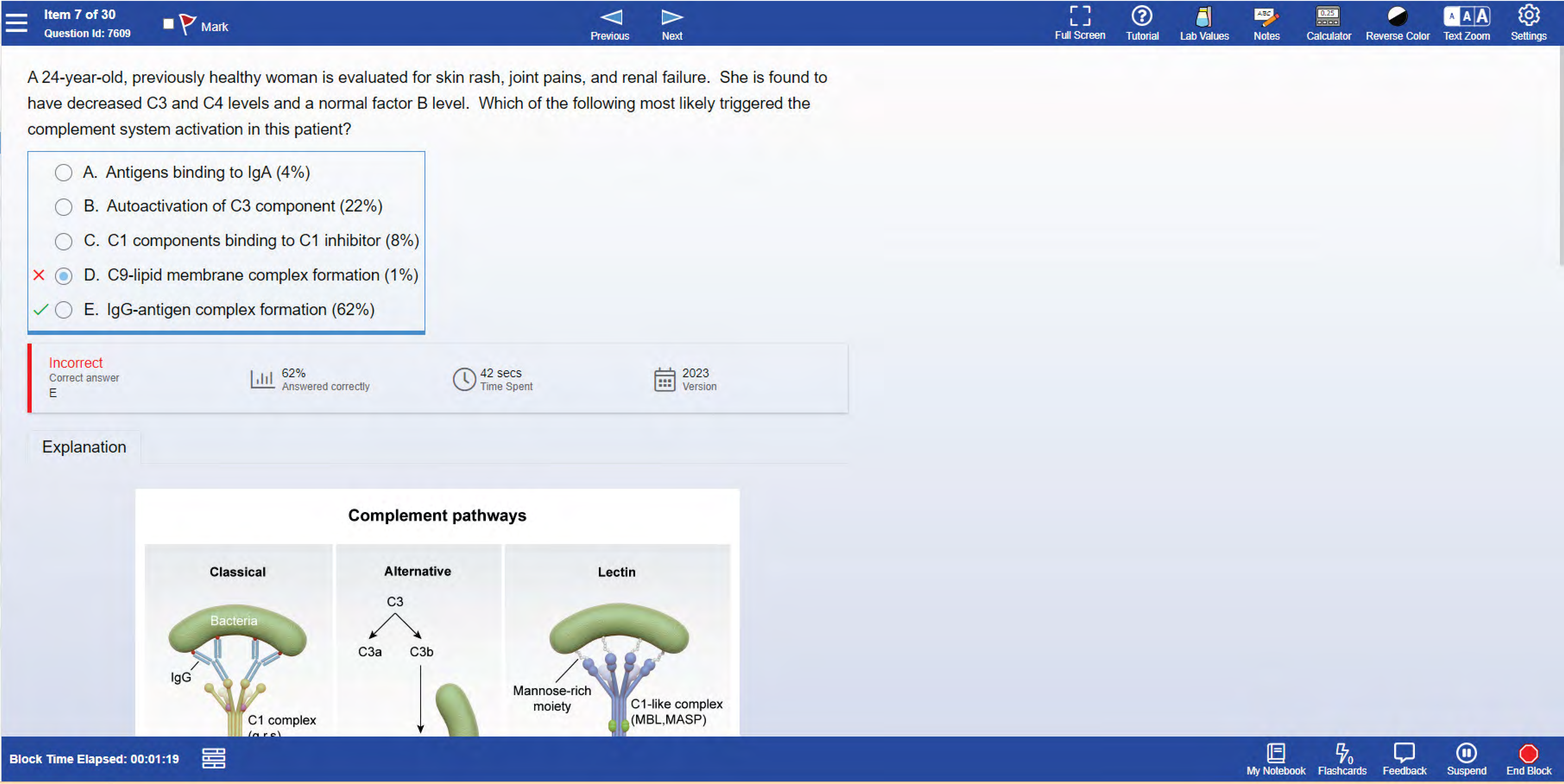
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- ○ A. Antigens binding to IgA (4%)
- ○ B. Autoactivation of C3 component (22%)
- ○ C. C1 components binding to C1 inhibitor (8%)
- ✗ ● D. C9-lipid membrane complex formation (1%)
- ✓ ○ E. IgG-antigen complex formation (62%)

Incorrect
Correct answer
E

62%
Answered correctly

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Time Spent

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Explanation

Complement pathways

Classical
Bacteria
IgG
C1 complex
(q,r,s)
Alternative
C3
C3a
C3b
Lectin
Mannose-rich
moiety
C1-like complex
(MBL,MASP)

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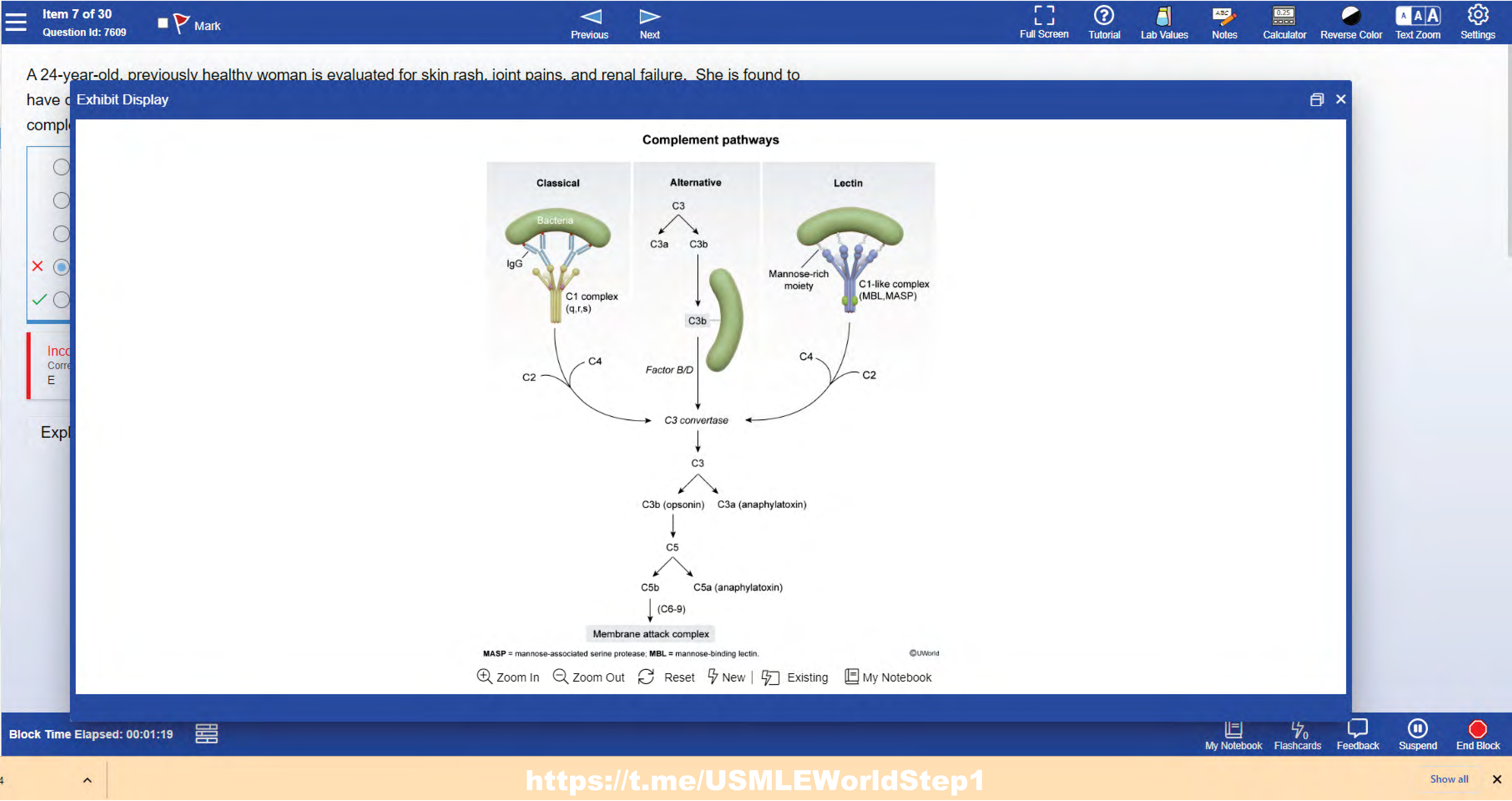
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Complement pathways

Classical
Bacteria
IgG
C1 complex (q,r,s)
C2
C4
Alternative
C3
C3a
C3b
C3b
Factor B/D
Lectin
Mannose-rich moiety
C1-like complex (MBL,MASP)
C4
C2
C3 convertase
C3
C3b (opsonin)
C3a (anaphylatoxin)
C5
C5b
C5a (anaphylatoxin)
(C6-9)
Membrane attack complex

MASP = mannose-associated serine protease; **MBL** = mannose-binding lectin.

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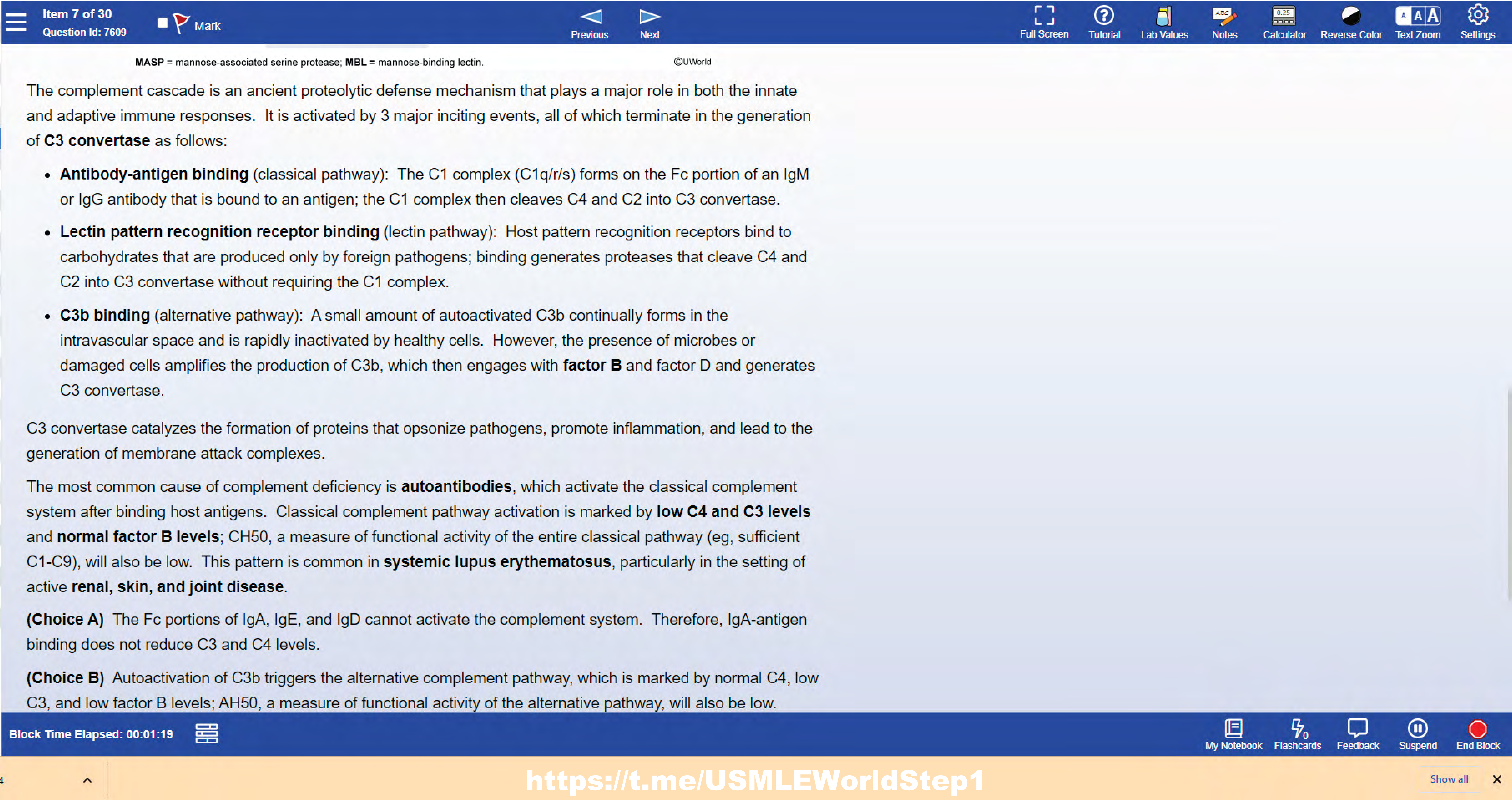

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The complement cascade is an ancient proteolytic defense mechanism that plays a major role in both the innate and adaptive immune responses. It is activated by 3 major inciting events, all of which terminate in the generation of **C3 convertase** as follows:

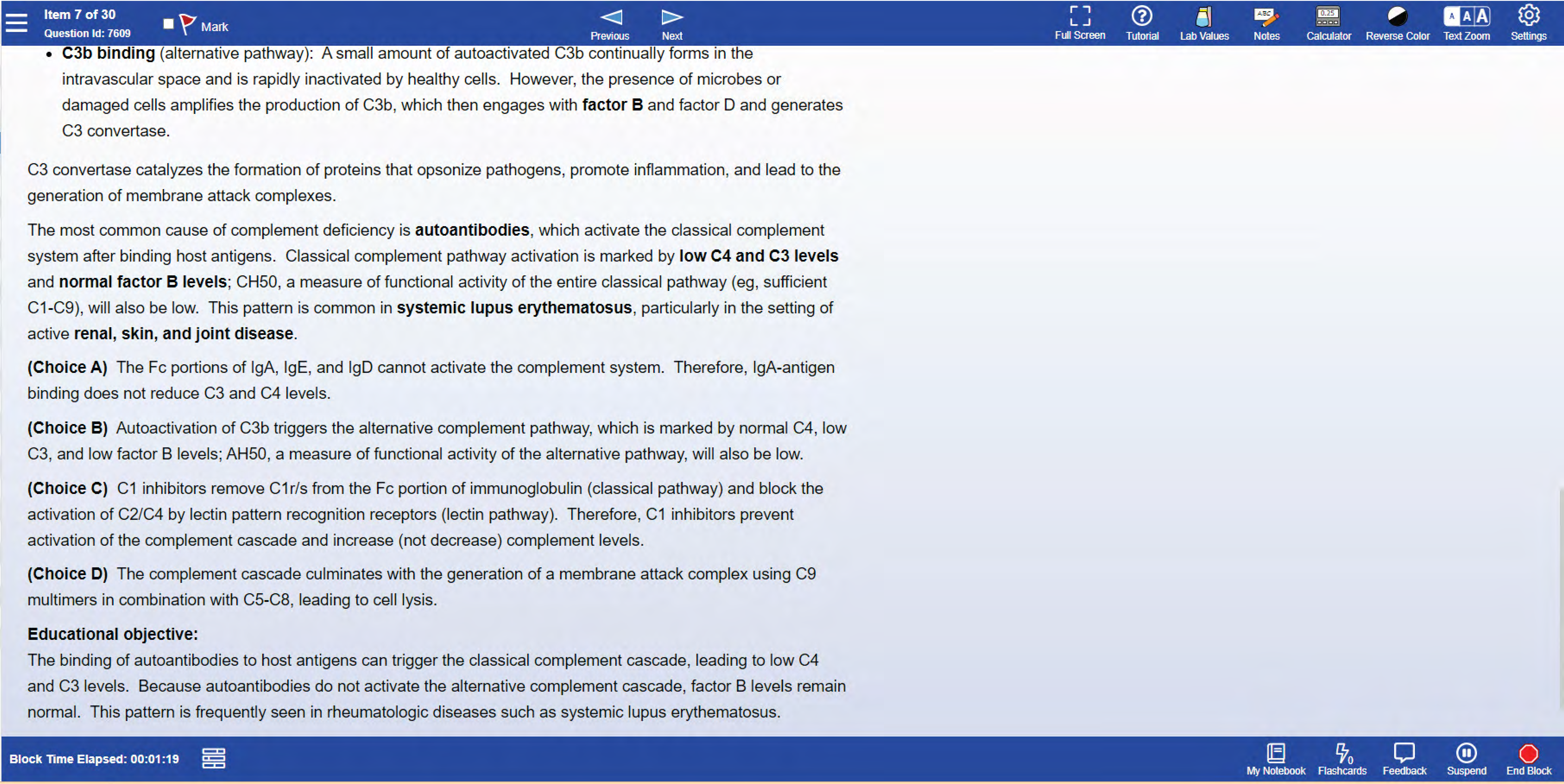
- **Antibody-antigen binding** (classical pathway): The C1 complex (C1q/r/s) forms on the Fc portion of an IgM or IgG antibody that is bound to an antigen; the C1 complex then cleaves C4 and C2 into C3 convertase.
- **Lectin pattern recognition receptor binding** (lectin pathway): Host pattern recognition receptors bind to carbohydrates that are produced only by foreign pathogens; binding generates proteases that cleave C4 and C2 into C3 convertase without requiring the C1 complex.
- **C3b binding** (alternative pathway): A small amount of autoactivated C3b continually forms in the intravascular space and is rapidly inactivated by healthy cells. However, the presence of microbes or damaged cells amplifies the production of C3b, which then engages with **factor B** and factor D and generates C3 convertase.

C3 convertase catalyzes the formation of proteins that opsonize pathogens, promote inflammation, and lead to the generation of membrane attack complexes.

The most common cause of complement deficiency is **autoantibodies**, which activate the classical complement system after binding host antigens. Classical complement pathway activation is marked by **low C4 and C3 levels** and **normal factor B levels**; CH50, a measure of functional activity of the entire classical pathway (eg, sufficient C1-C9), will also be low. This pattern is common in **systemic lupus erythematosus**, particularly in the setting of active **renal, skin, and joint disease**.

(Choice A) The Fc portions of IgA, IgE, and IgD cannot activate the complement system. Therefore, IgA-antigen binding does not reduce C3 and C4 levels.

(Choice B) Autoactivation of C3b triggers the alternative complement pathway, which is marked by normal C4, low C3, and low factor B levels; AH50, a measure of functional activity of the alternative pathway, will also be low.



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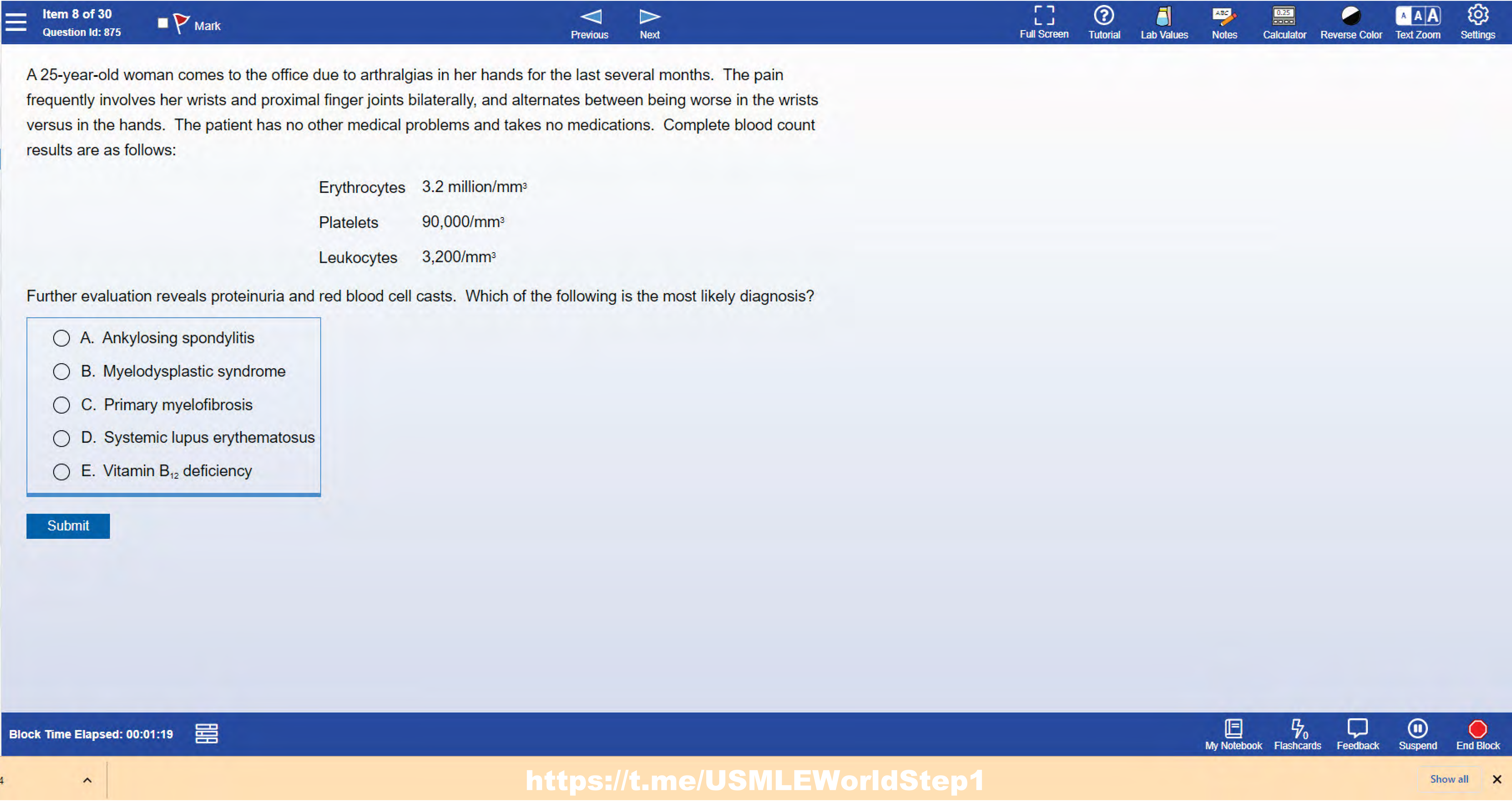
(Choice B) Autoactivation of C3b triggers the alternative complement pathway, which is marked by normal C4, low C3, and low factor B levels; AH50, a measure of functional activity of the alternative pathway, will also be low.

(Choice C) C1 inhibitors remove C1r/s from the Fc portion of immunoglobulin (classical pathway) and block the activation of C2/C4 by lectin pattern recognition receptors (lectin pathway). Therefore, C1 inhibitors prevent activation of the complement cascade and increase (not decrease) complement levels.

(Choice D) The complement cascade culminates with the generation of a membrane attack complex using C9 multimers in combination with C5-C8, leading to cell lysis.

Educational objective:

The binding of autoantibodies to host antigens can trigger the classical complement cascade, leading to low C4 and C3 levels. Because autoantibodies do not activate the alternative complement cascade, factor B levels remain normal. This pattern is frequently seen in rheumatologic diseases such as systemic lupus erythematosus.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A 25-year-old woman comes to the office due to arthralgias in her hands for the last several months. The pain frequently involves her wrists and proximal finger joints bilaterally, and alternates between being worse in the wrists versus in the hands. The patient has no other medical problems and takes no medications. Complete blood count results are as follows:

Erythrocytes	3.2 million/mm^3
Platelets	90,000/mm^3
Leukocytes	3,200/mm^3

Further evaluation reveals proteinuria and red blood cell casts. Which of the following is the most likely diagnosis?

○ A. Ankylosing spondylitis
○ B. Myelodysplastic syndrome
○ C. Primary myelofibrosis
○ D. Systemic lupus erythematosus
○ E. Vitamin B$_{12}$ deficiency

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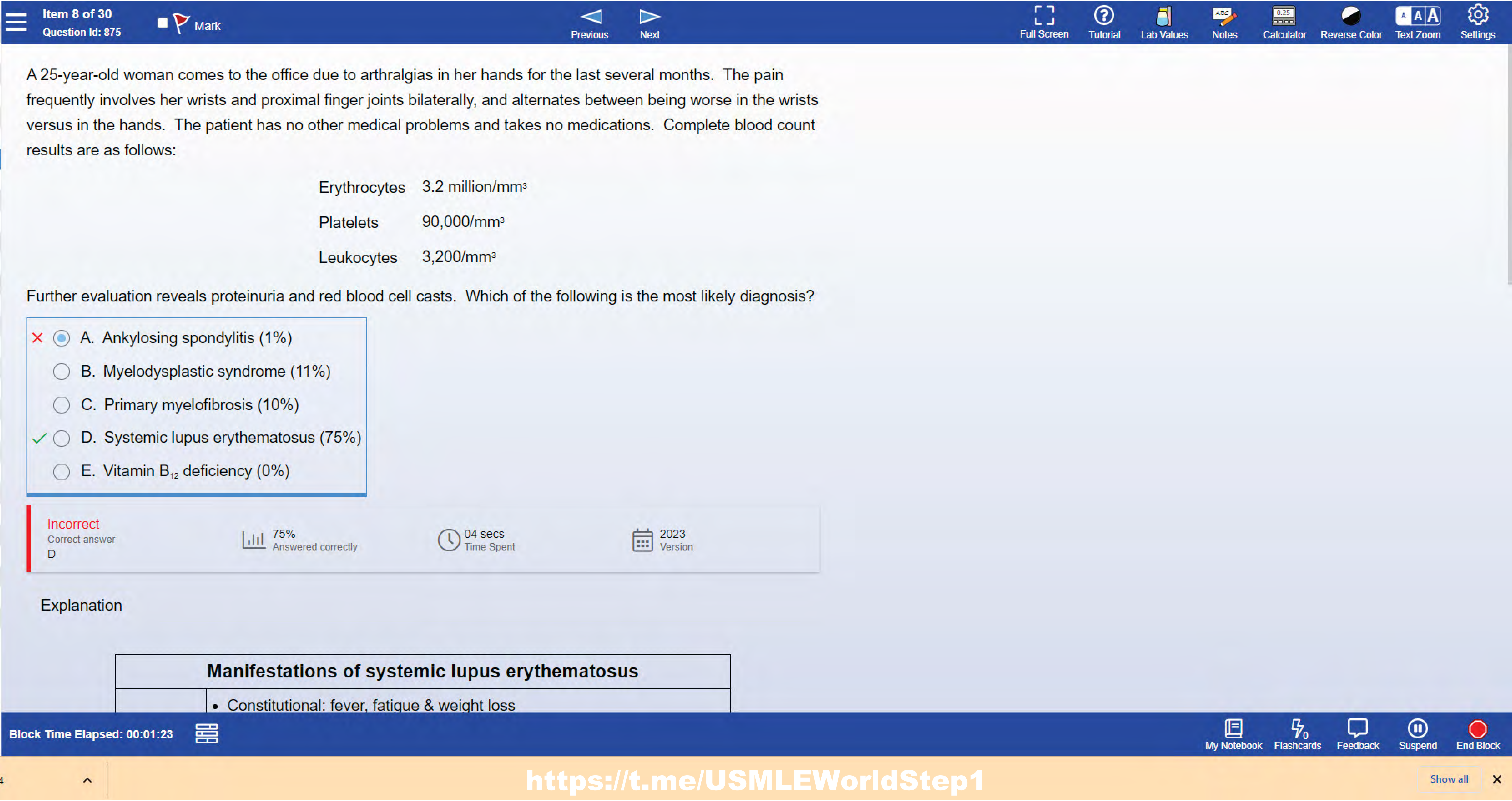
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Further evaluation reveals proteinuria and red blood cell casts. Which of the following is the most likely diagnosis?

✗ ● A. Ankylosing spondylitis (1%)
○ B. Myelodysplastic syndrome (11%)
○ C. Primary myelofibrosis (10%)
✓ ○ D. Systemic lupus erythematosus (75%)
○ E. Vitamin B_{12} deficiency (0%)

Incorrect
Correct answer
D

75%
Answered correctly

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Explanation

Manifestations of systemic lupus erythematosus	
	• Constitutional: fever, fatigue & weight loss

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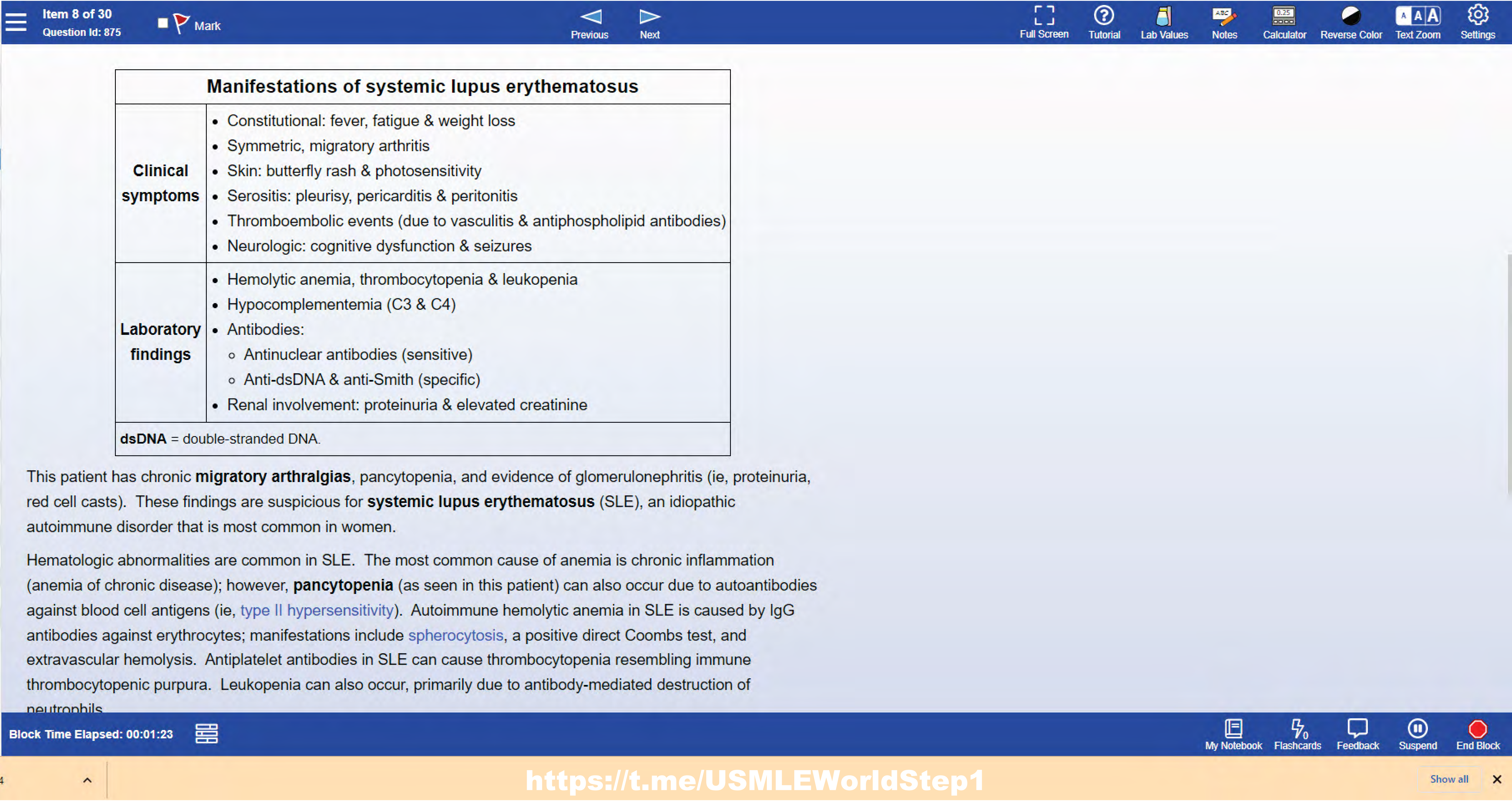
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Manifestations of systemic lupus erythematosus

Clinical symptoms	• Constitutional: fever, fatigue & weight loss • Symmetric, migratory arthritis • Skin: butterfly rash & photosensitivity • Serositis: pleurisy, pericarditis & peritonitis • Thromboembolic events (due to vasculitis & antiphospholipid antibodies) • Neurologic: cognitive dysfunction & seizures
Laboratory findings	• Hemolytic anemia, thrombocytopenia & leukopenia • Hypocomplementemia (C3 & C4) • Antibodies: ◦ Antinuclear antibodies (sensitive) ◦ Anti-dsDNA & anti-Smith (specific) • Renal involvement: proteinuria & elevated creatinine

dsDNA = double-stranded DNA.

This patient has chronic **migratory arthralgias**, pancytopenia, and evidence of glomerulonephritis (ie, proteinuria, red cell casts). These findings are suspicious for **systemic lupus erythematosus** (SLE), an idiopathic autoimmune disorder that is most common in women.

Hematologic abnormalities are common in SLE. The most common cause of anemia is chronic inflammation (anemia of chronic disease); however, **pancytopenia** (as seen in this patient) can also occur due to autoantibodies against blood cell antigens (ie, type II hypersensitivity). Autoimmune hemolytic anemia in SLE is caused by IgG antibodies against erythrocytes; manifestations include spherocytosis, a positive direct Coombs test, and extravascular hemolysis. Antiplatelet antibodies in SLE can cause thrombocytopenia resembling immune thrombocytopenic purpura. Leukopenia can also occur, primarily due to antibody-mediated destruction of neutrophils

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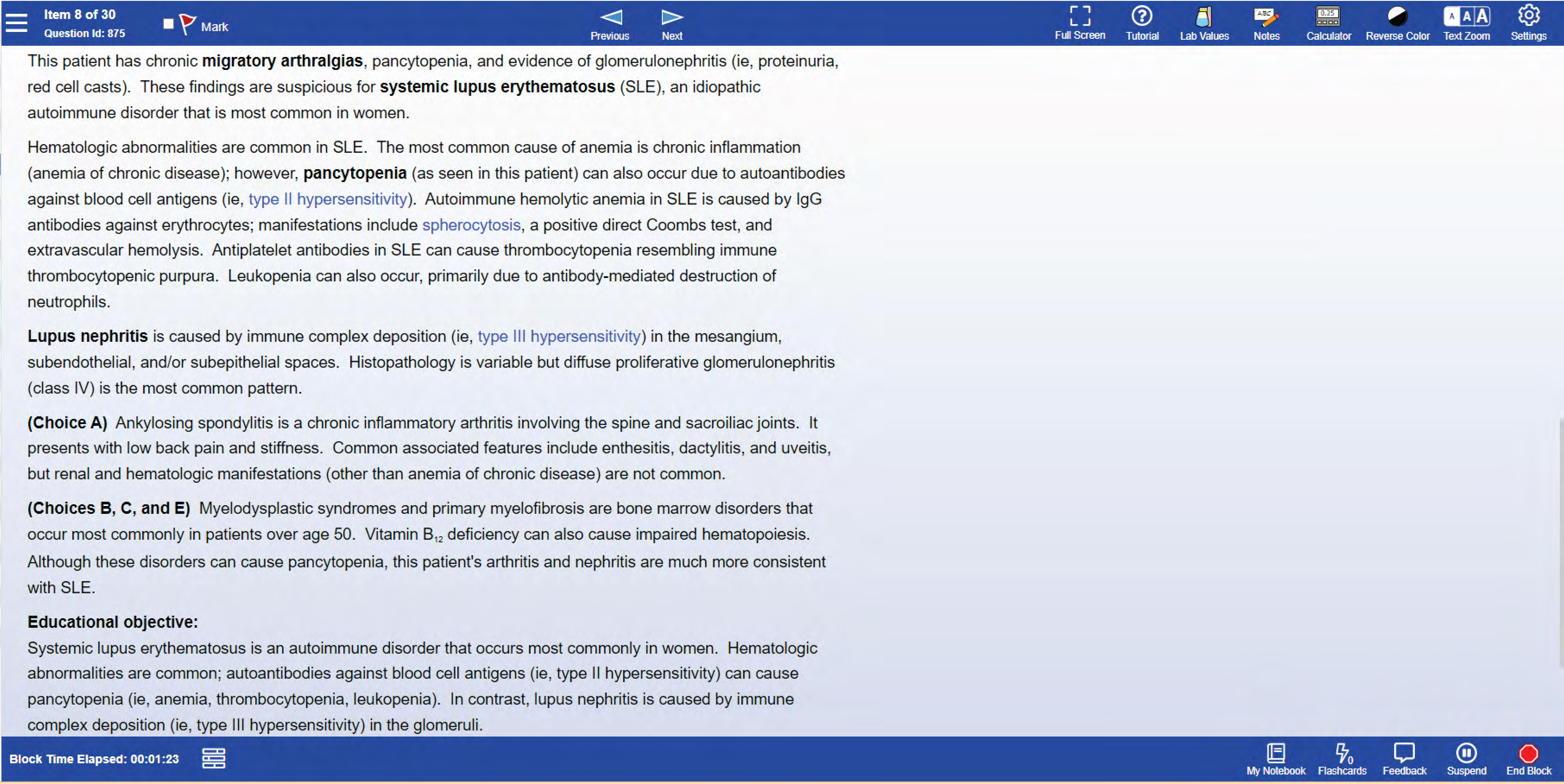

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Lupus nephritis is caused by immune complex deposition (ie, type III hypersensitivity) in the mesangium, subendothelial, and/or subepithelial spaces. Histopathology is variable but diffuse proliferative glomerulonephritis (class IV) is the most common pattern.

(Choice A) Ankylosing spondylitis is a chronic inflammatory arthritis involving the spine and sacroiliac joints. It presents with low back pain and stiffness. Common associated features include enthesitis, dactylitis, and uveitis, but renal and hematologic manifestations (other than anemia of chronic disease) are not common.

(Choices B, C, and E) Myelodysplastic syndromes and primary myelofibrosis are bone marrow disorders that occur most commonly in patients over age 50. Vitamin B_{12} deficiency can also cause impaired hematopoiesis. Although these disorders can cause pancytopenia, this patient's arthritis and nephritis are much more consistent with SLE.

Educational objective:
Systemic lupus erythematosus is an autoimmune disorder that occurs most commonly in women. Hematologic abnormalities are common; autoantibodies against blood cell antigens (ie, type II hypersensitivity) can cause pancytopenia (ie, anemia, thrombocytopenia, leukopenia). In contrast, lupus nephritis is caused by immune complex deposition (ie, type III hypersensitivity) in the glomeruli.

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This patient has chronic **migratory arthralgias**, pancytopenia, and evidence of glomerulonephritis (ie, proteinuria,

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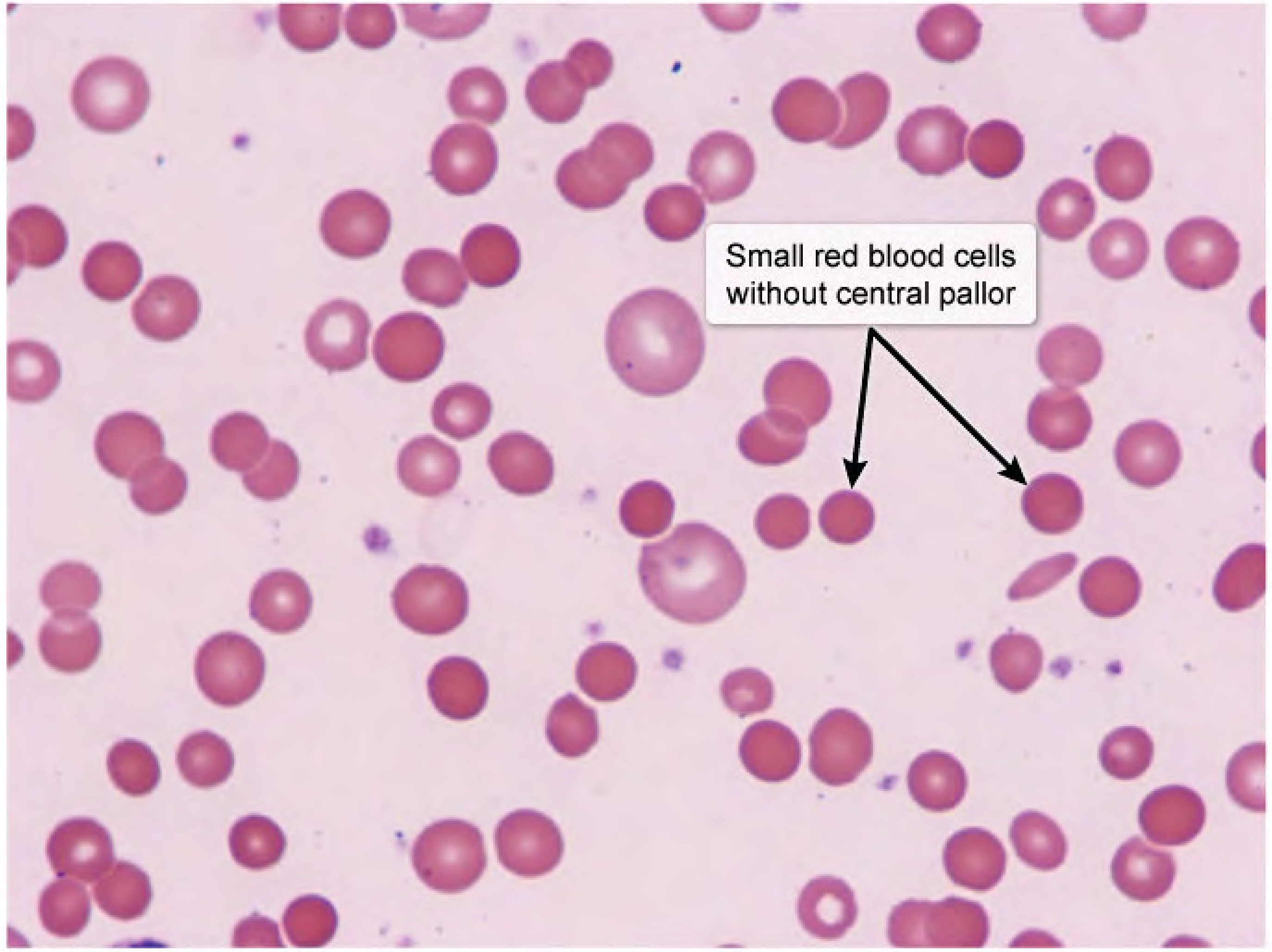

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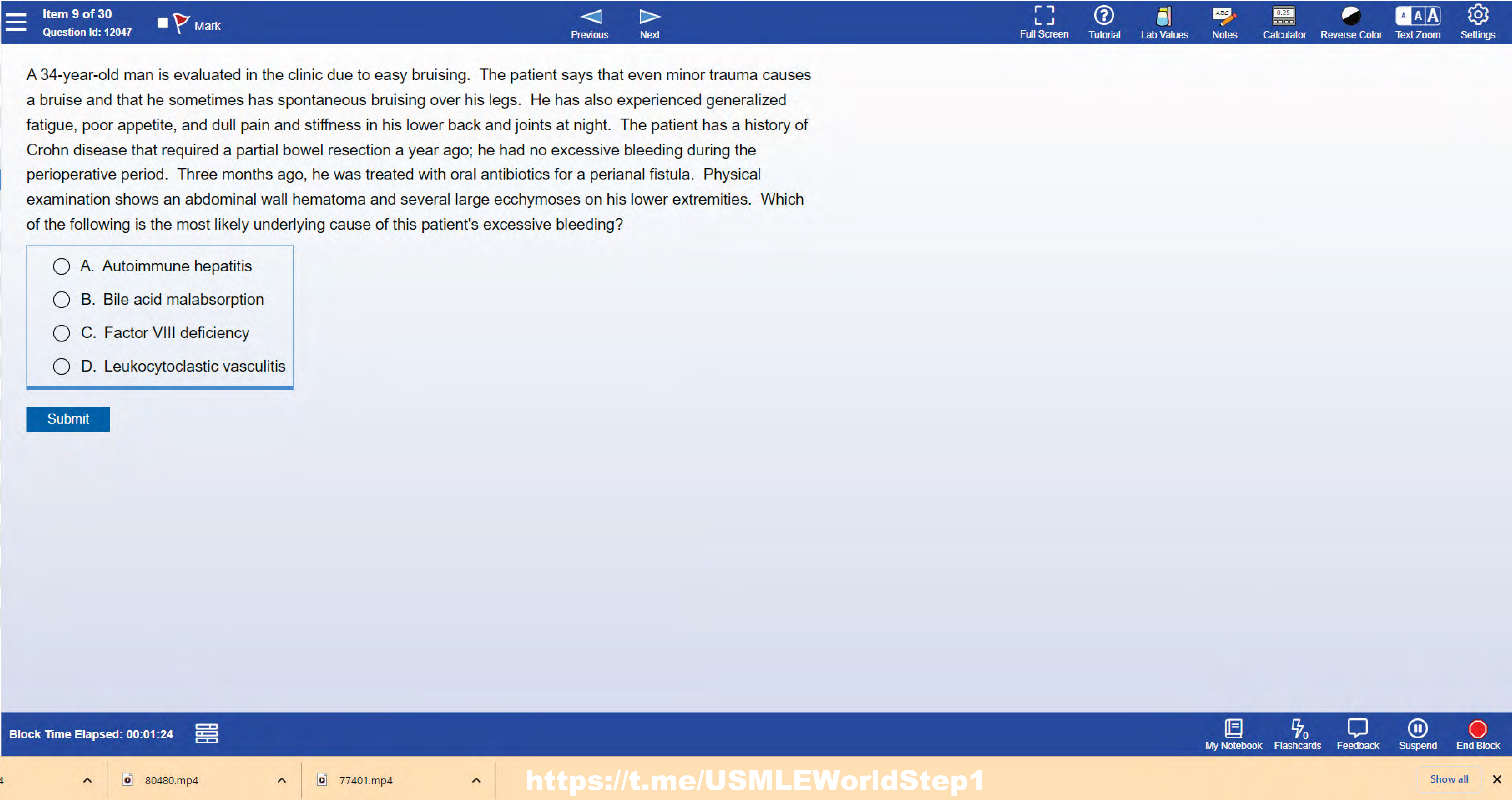
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A 34-year-old man is evaluated in the clinic due to easy bruising. The patient says that even minor trauma causes a bruise and that he sometimes has spontaneous bruising over his legs. He has also experienced generalized fatigue, poor appetite, and dull pain and stiffness in his lower back and joints at night. The patient has a history of Crohn disease that required a partial bowel resection a year ago; he had no excessive bleeding during the perioperative period. Three months ago, he was treated with oral antibiotics for a perianal fistula. Physical examination shows an abdominal wall hematoma and several large ecchymoses on his lower extremities. Which of the following is the most likely underlying cause of this patient's excessive bleeding?

○ A. Autoimmune hepatitis
○ B. Bile acid malabsorption
○ C. Factor VIII deficiency
○ D. Leukocytoclastic vasculitis

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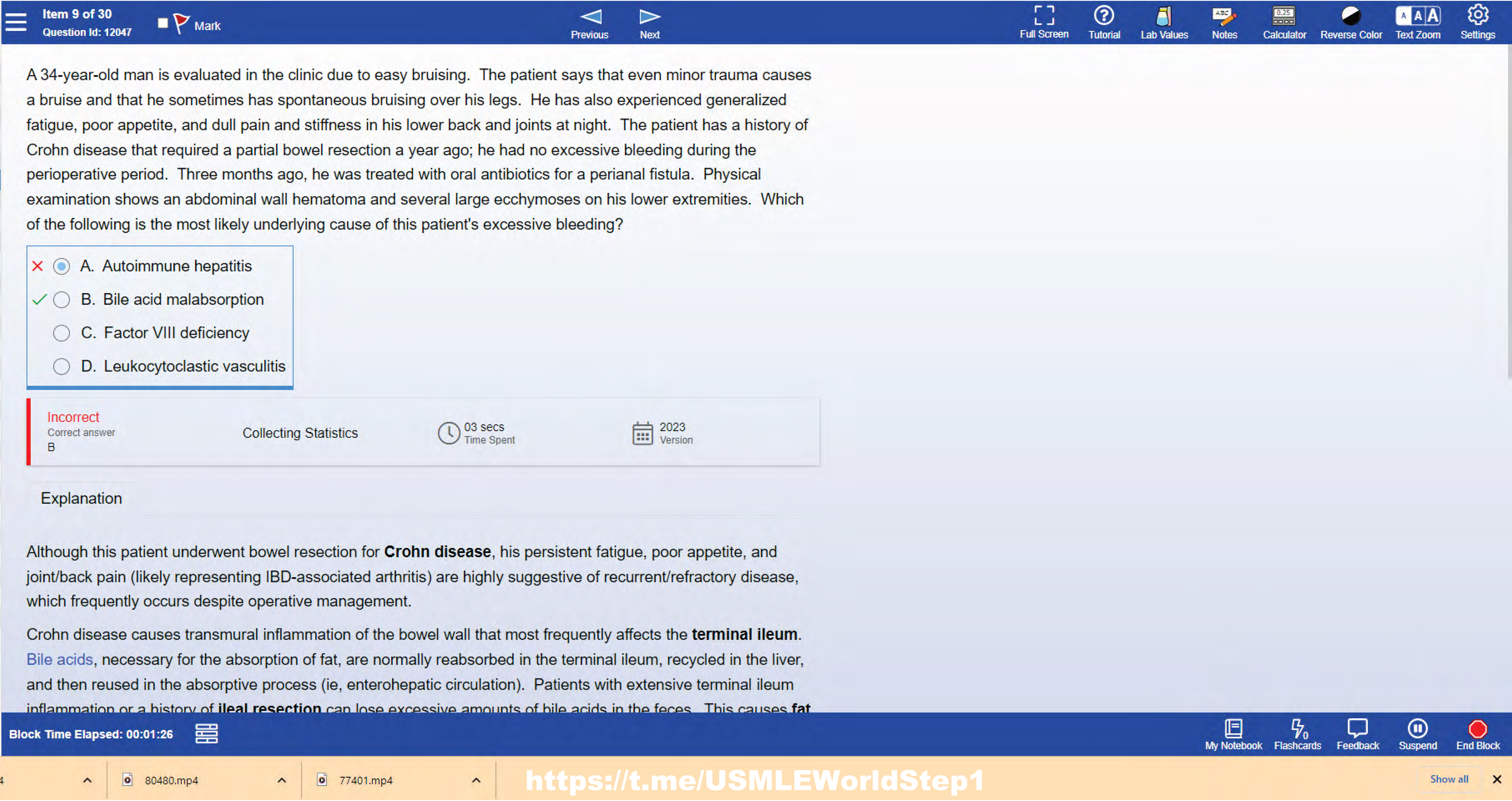
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○ C. Factor VIII deficiency
○ D. Leukocytoclastic vasculitis

Incorrect
Correct answer
B

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Explanation

Although this patient underwent bowel resection for **Crohn disease**, his persistent fatigue, poor appetite, and joint/back pain (likely representing IBD-associated arthritis) are highly suggestive of recurrent/refractory disease, which frequently occurs despite operative management.

Crohn disease causes transmural inflammation of the bowel wall that most frequently affects the **terminal ileum**. Bile acids, necessary for the absorption of fat, are normally reabsorbed in the terminal ileum, recycled in the liver, and then reused in the absorptive process (ie, enterohepatic circulation). Patients with extensive terminal ileum inflammation or a history of **ileal resection** can lose excessive amounts of bile acids in the feces. This causes **fat**

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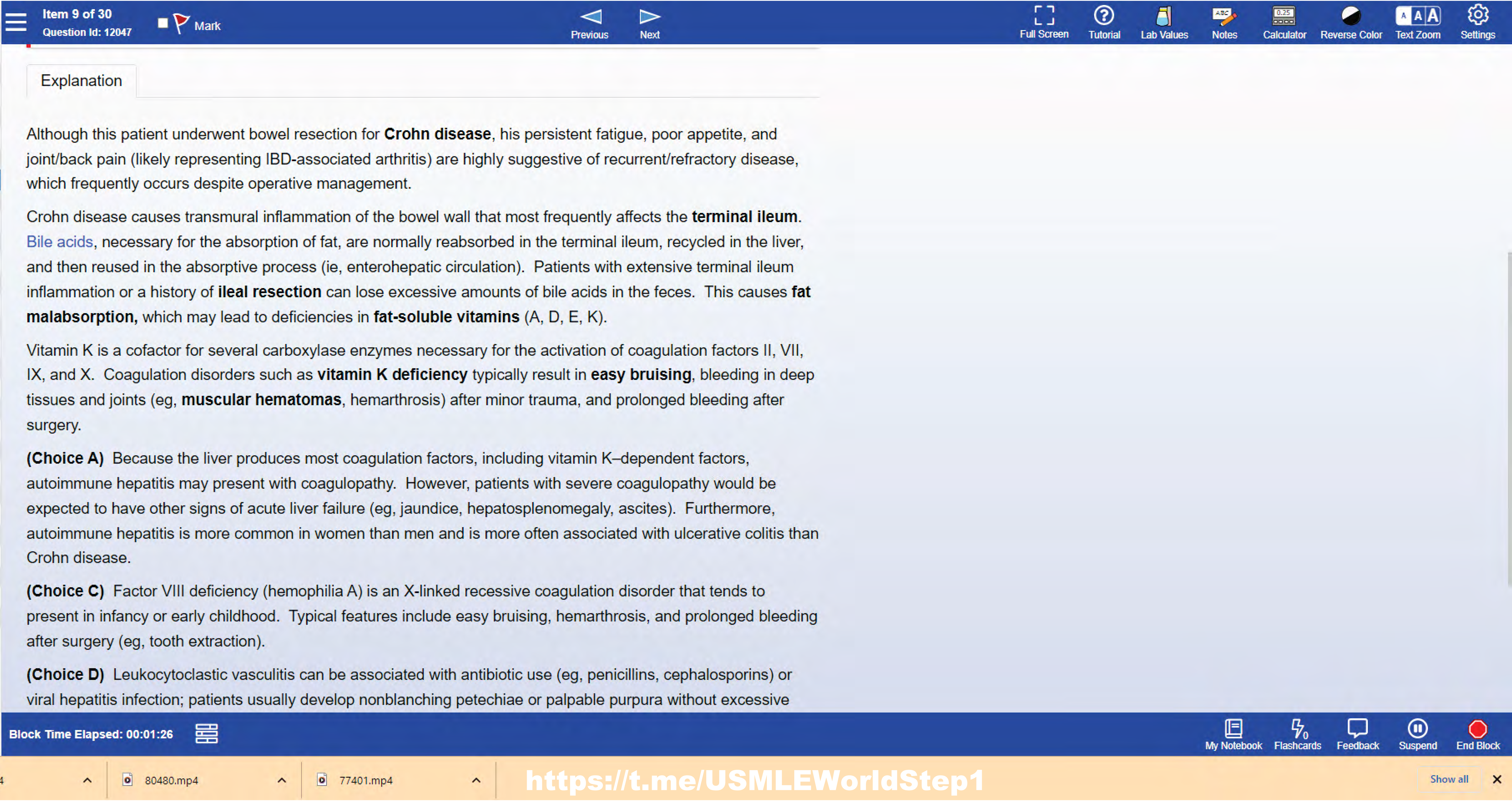
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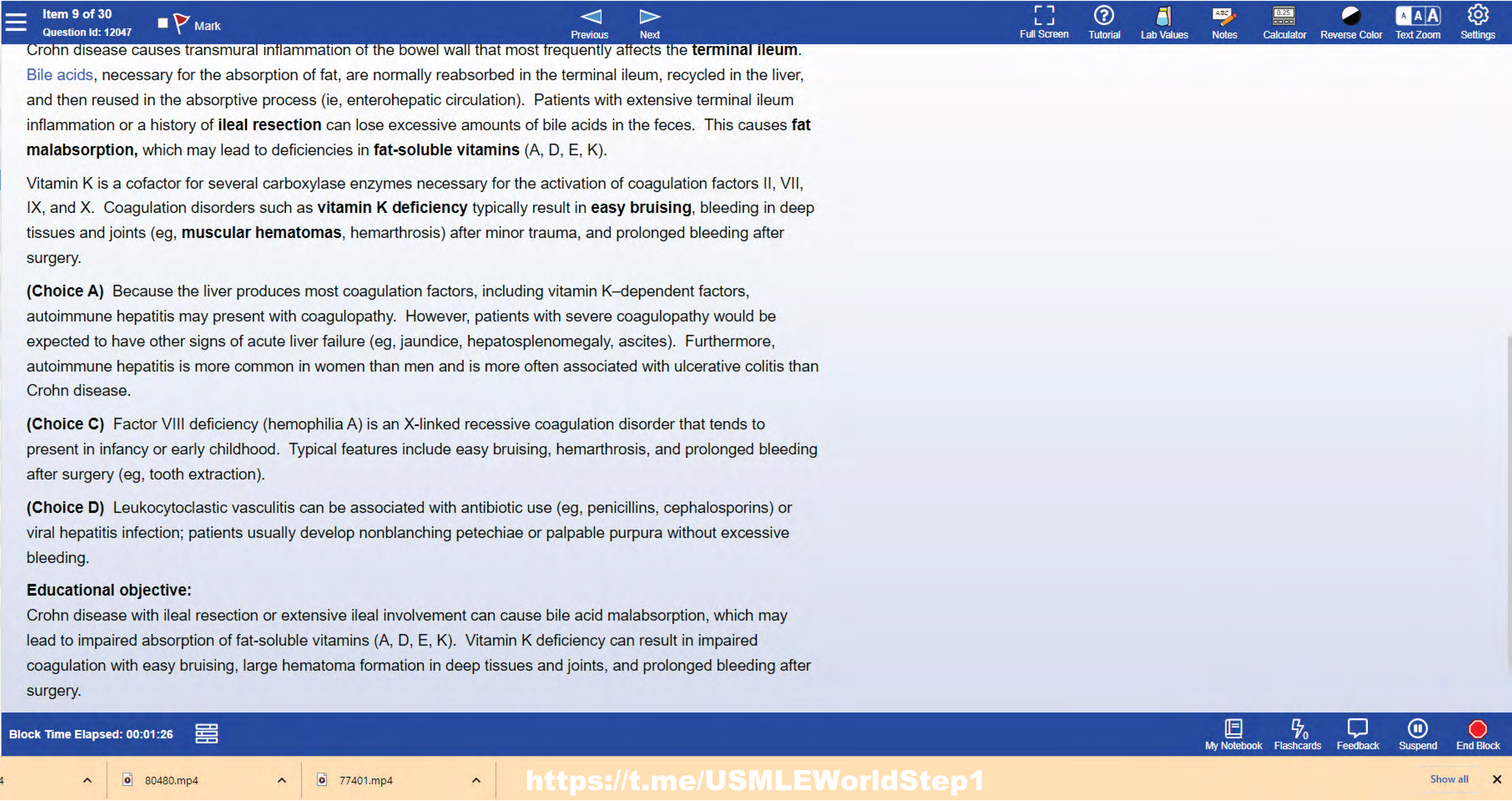
Vitamin K is a cofactor for several carboxylase enzymes necessary for the activation of coagulation factors II, VII, IX, and X. Coagulation disorders such as **vitamin K deficiency** typically result in **easy bruising**, bleeding in deep tissues and joints (eg, **muscular hematomas**, hemarthrosis) after minor trauma, and prolonged bleeding after surgery.

(Choice A) Because the liver produces most coagulation factors, including vitamin K–dependent factors, autoimmune hepatitis may present with coagulopathy. However, patients with severe coagulopathy would be expected to have other signs of acute liver failure (eg, jaundice, hepatosplenomegaly, ascites). Furthermore, autoimmune hepatitis is more common in women than men and is more often associated with ulcerative colitis than Crohn disease.

(Choice C) Factor VIII deficiency (hemophilia A) is an X-linked recessive coagulation disorder that tends to present in infancy or early childhood. Typical features include easy bruising, hemarthrosis, and prolonged bleeding after surgery (eg, tooth extraction).

(Choice D) Leukocytoclastic vasculitis can be associated with antibiotic use (eg, penicillins, cephalosporins) or viral hepatitis infection; patients usually develop nonblanching petechiae or palpable purpura without excessive



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Educational objective:

Crohn disease with ileal resection or extensive ileal involvement can cause bile acid malabsorption, which may lead to impaired absorption of fat-soluble vitamins (A, D, E, K). Vitamin K deficiency can result in impaired coagulation with easy bruising, large hematoma formation in deep tissues and joints, and prolonged bleeding after surgery.

Crohn disease causes transmural inflammation of the bowel wall that most frequently affects the **terminal ileum**.

Bile acids, necessary for the absorption of fat, are normally reabsorbed in the terminal ileum, recycled in the liver

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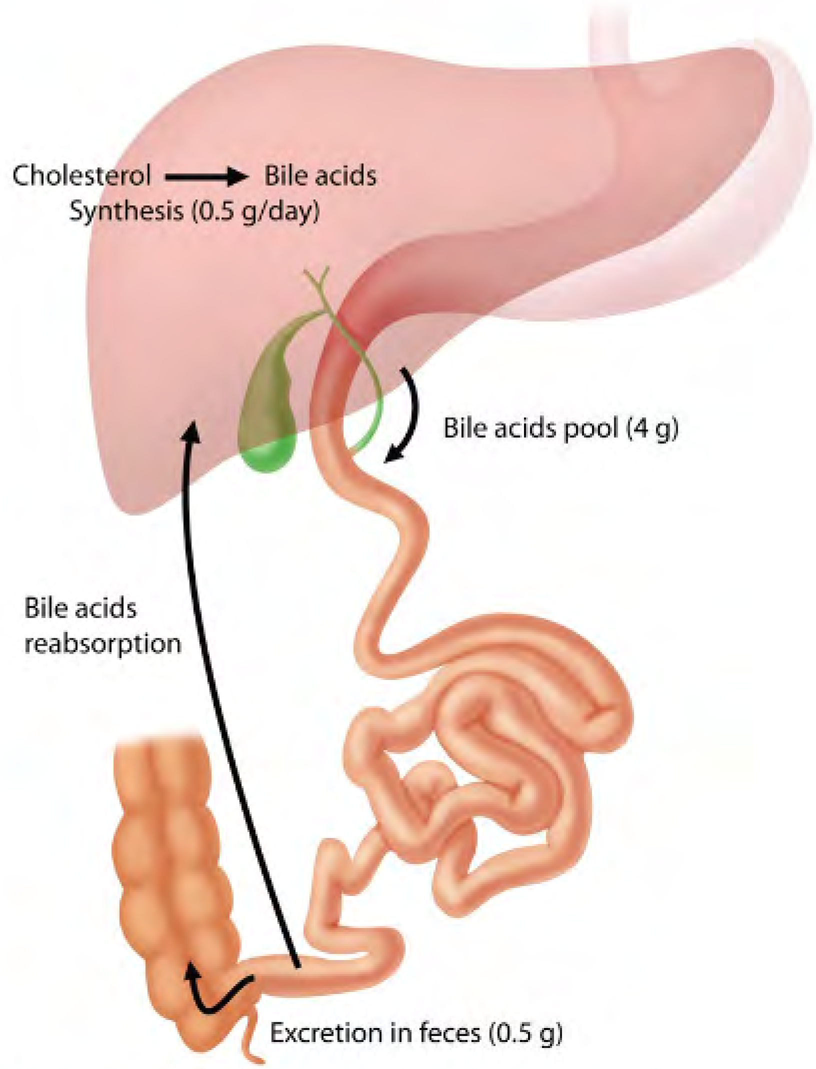
Bile acid metabolism


Cholesterol → Bile acids
Synthesis (0.5 g/day)
Bile acids pool (4 g)
Bile acids
reabsorption
Excretion in feces (0.5 g)

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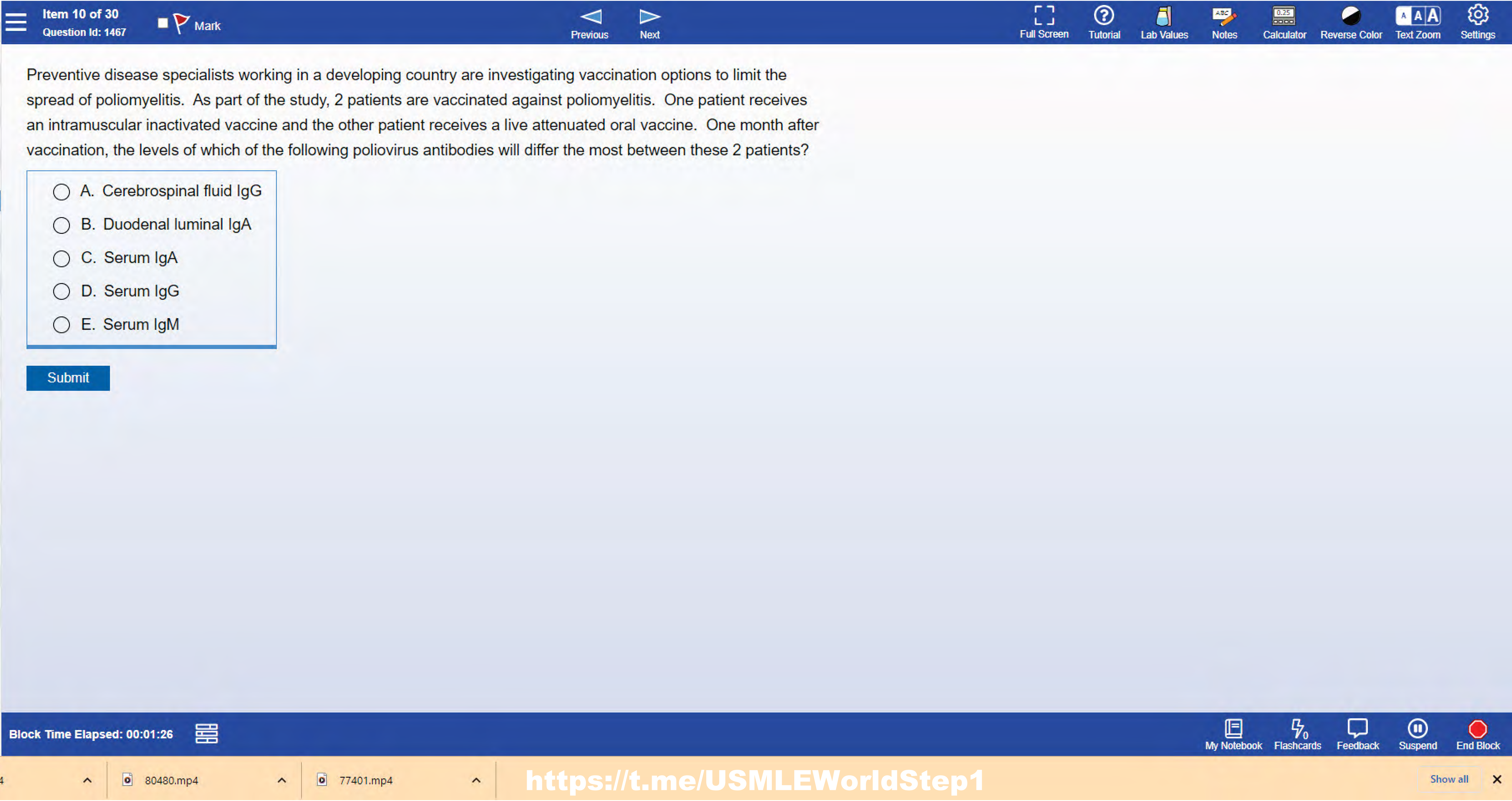
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Preventive disease specialists working in a developing country are investigating vaccination options to limit the spread of poliomyelitis. As part of the study, 2 patients are vaccinated against poliomyelitis. One patient receives an intramuscular inactivated vaccine and the other patient receives a live attenuated oral vaccine. One month after vaccination, the levels of which of the following poliovirus antibodies will differ the most between these 2 patients?

○ A. Cerebrospinal fluid IgG
○ B. Duodenal luminal IgA
○ C. Serum IgA
○ D. Serum IgG
○ E. Serum IgM

Submit

Preventive disease specialists working in a developing country are investigating vaccination options to limit the spread of poliomyelitis. As part of the study, 2 patients are vaccinated against poliomyelitis. One patient receives an intramuscular inactivated vaccine and the other patient receives a live attenuated oral vaccine. One month after vaccination, the levels of which of the following poliovirus antibodies will differ the most between these 2 patients?

✗ ● A. Cerebrospinal fluid IgG (3%)
✓ ○ B. Duodenal luminal IgA (49%)
○ C. Serum IgA (12%)
○ D. Serum IgG (27%)
○ E. Serum IgM (7%)

Incorrect
Correct answer
B

49%
Answered correctly

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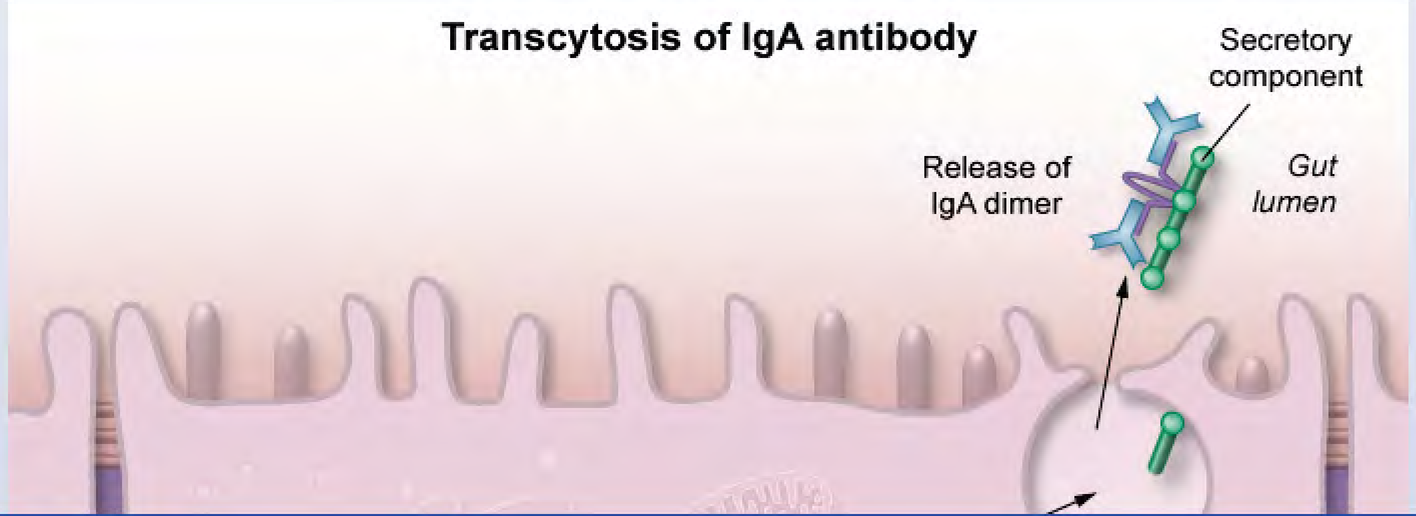
Explanation


Transcytosis of IgA antibody

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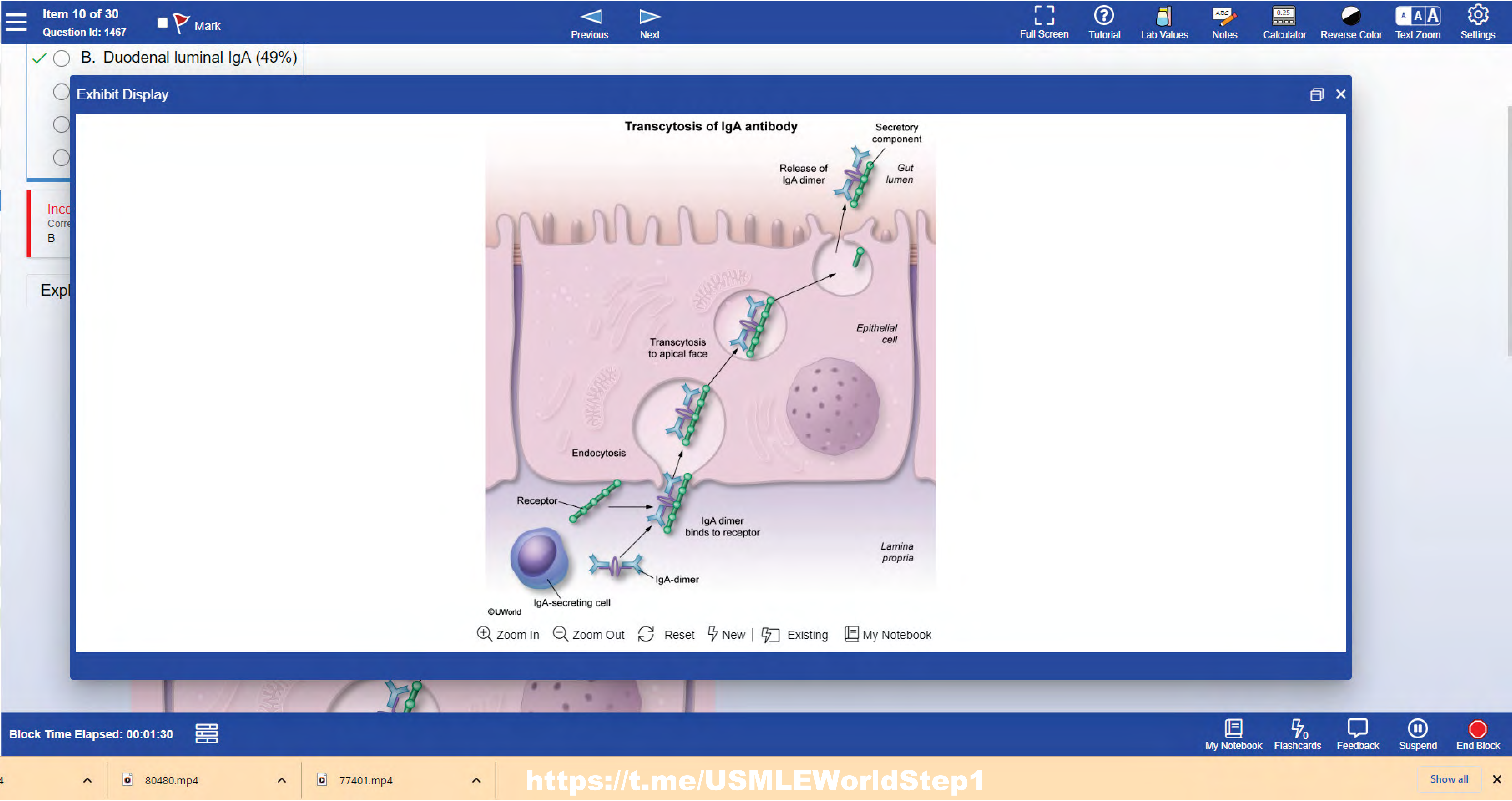

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✓ ○ B. Duodenal luminal IgA (49%)

Exhibit Display

Transcytosis of IgA antibody

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Secretory component
Release of IgA dimer
Gut lumen
Transcytosis to apical face
Epithelial cell
Endocytosis
Receptor
IgA dimer binds to receptor
Lamina propria
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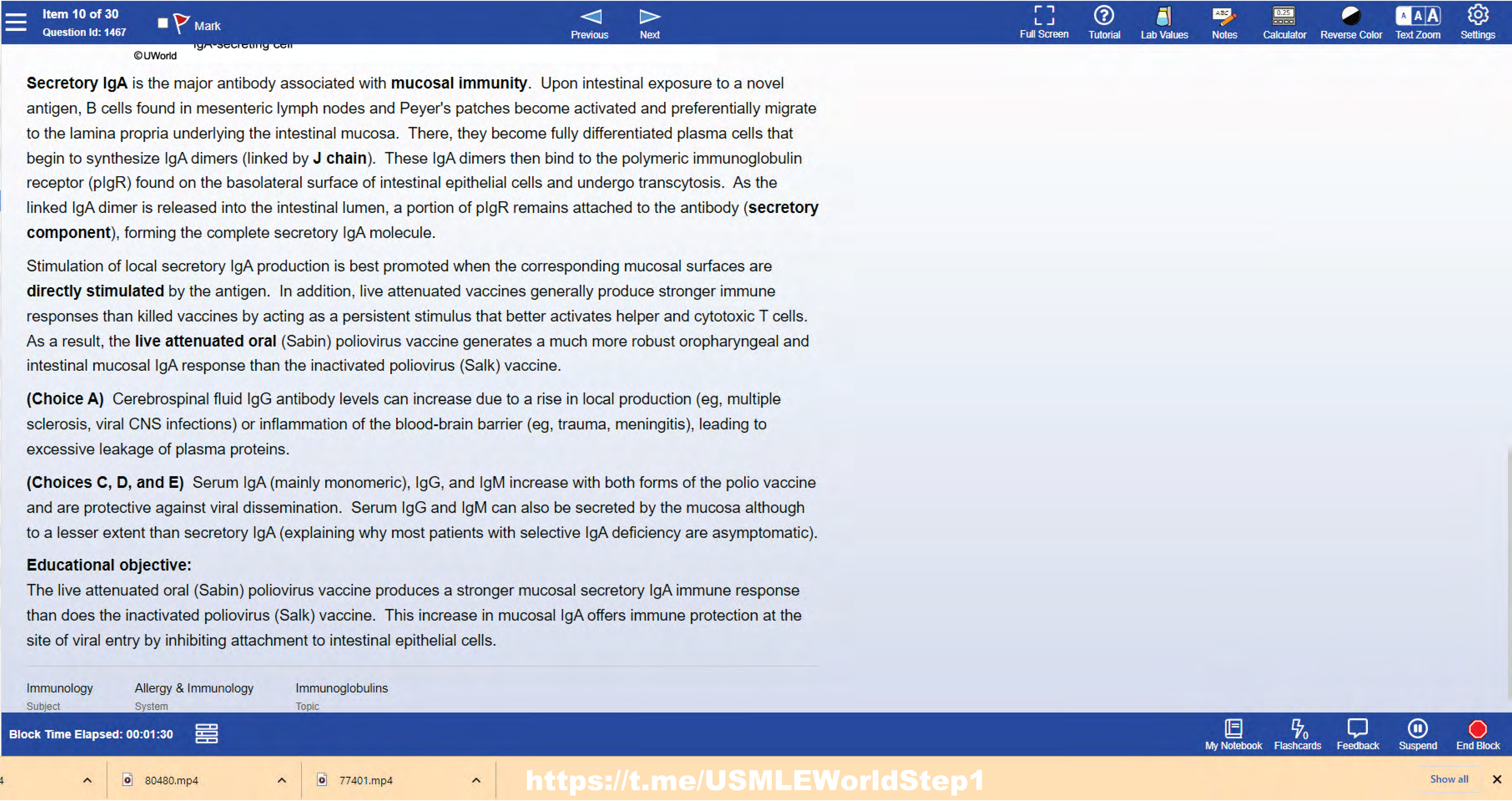
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IgA-secreting cell
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Secretory IgA is the major antibody associated with **mucosal immunity**. Upon intestinal exposure to a novel antigen, B cells found in mesenteric lymph nodes and Peyer's patches become activated and preferentially migrate to the lamina propria underlying the intestinal mucosa. There, they become fully differentiated plasma cells that begin to synthesize IgA dimers (linked by **J chain**). These IgA dimers then bind to the polymeric immunoglobulin receptor (pIgR) found on the basolateral surface of intestinal epithelial cells and undergo transcytosis. As the linked IgA dimer is released into the intestinal lumen, a portion of pIgR remains attached to the antibody (**secretory component**), forming the complete secretory IgA molecule.

Stimulation of local secretory IgA production is best promoted when the corresponding mucosal surfaces are **directly stimulated** by the antigen. In addition, live attenuated vaccines generally produce stronger immune responses than killed vaccines by acting as a persistent stimulus that better activates helper and cytotoxic T cells. As a result, the **live attenuated oral** (Sabin) poliovirus vaccine generates a much more robust oropharyngeal and intestinal mucosal IgA response than the inactivated poliovirus (Salk) vaccine.

(Choice A) Cerebrospinal fluid IgG antibody levels can increase due to a rise in local production (eg, multiple sclerosis, viral CNS infections) or inflammation of the blood-brain barrier (eg, trauma, meningitis), leading to excessive leakage of plasma proteins.

(Choices C, D, and E) Serum IgA (mainly monomeric), IgG, and IgM increase with both forms of the polio vaccine and are protective against viral dissemination. Serum IgG and IgM can also be secreted by the mucosa although to a lesser extent than secretory IgA (explaining why most patients with selective IgA deficiency are asymptomatic).

Educational objective:

The live attenuated oral (Sabin) poliovirus vaccine produces a stronger mucosal secretory IgA immune response than does the inactivated poliovirus (Salk) vaccine. This increase in mucosal IgA offers immune protection at the site of viral entry by inhibiting attachment to intestinal epithelial cells.

Immunology	Allergy & Immunology	Immunoglobulins
Subject	System	Topic

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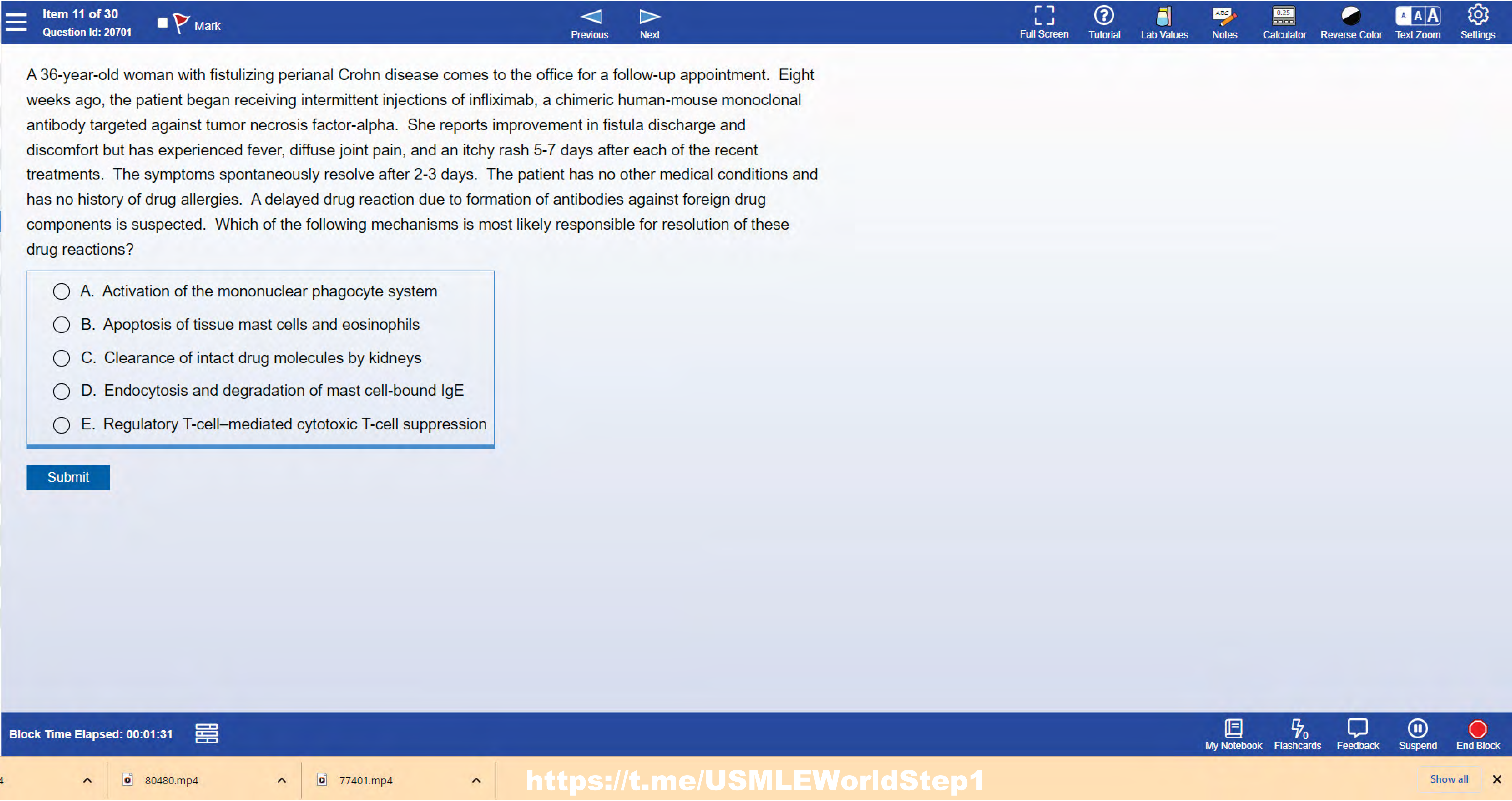
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A 36-year-old woman with fistulizing perianal Crohn disease comes to the office for a follow-up appointment. Eight weeks ago, the patient began receiving intermittent injections of infliximab, a chimeric human-mouse monoclonal antibody targeted against tumor necrosis factor-alpha. She reports improvement in fistula discharge and discomfort but has experienced fever, diffuse joint pain, and an itchy rash 5-7 days after each of the recent treatments. The symptoms spontaneously resolve after 2-3 days. The patient has no other medical conditions and has no history of drug allergies. A delayed drug reaction due to formation of antibodies against foreign drug components is suspected. Which of the following mechanisms is most likely responsible for resolution of these drug reactions?

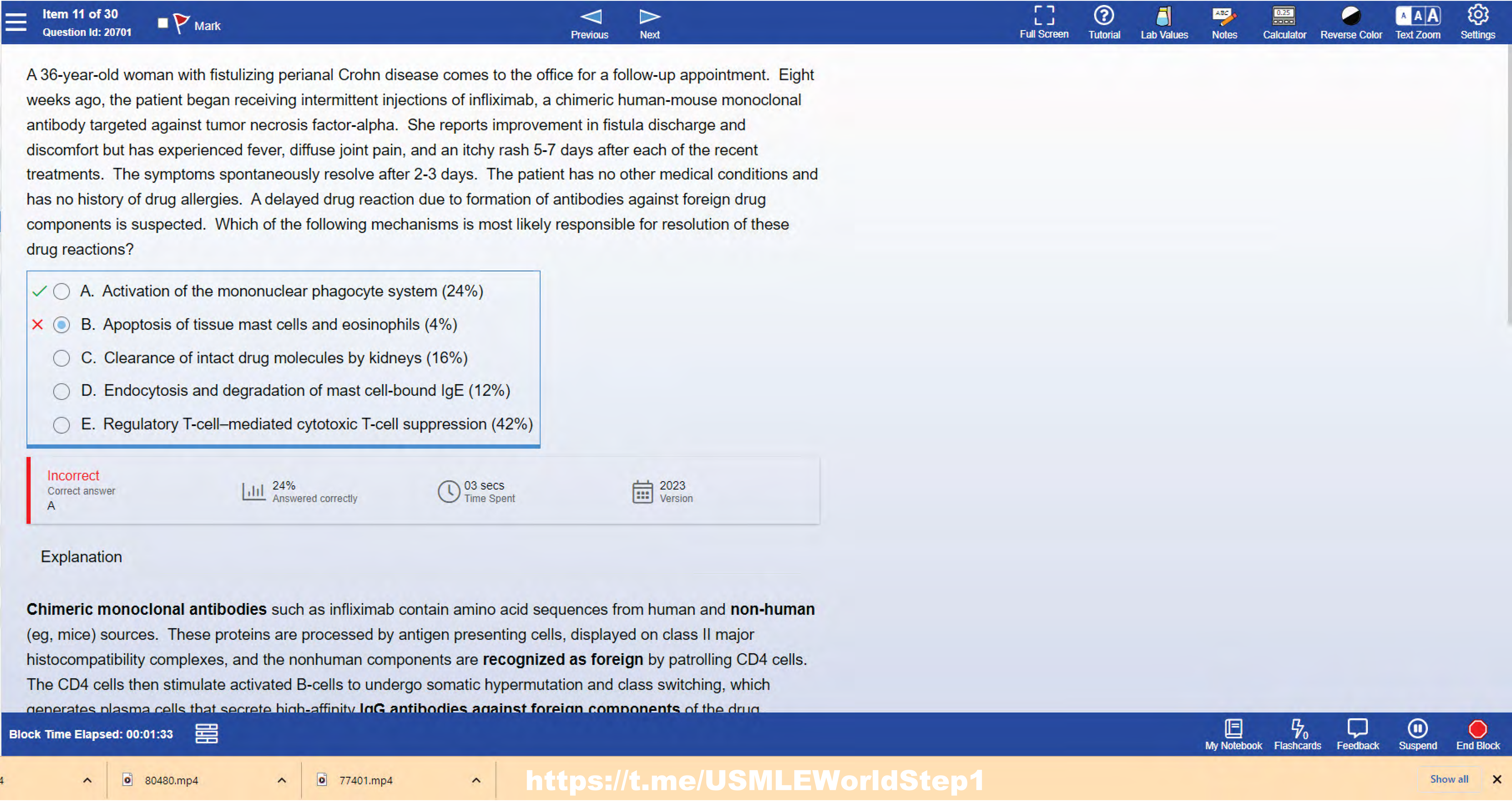
○ A. Activation of the mononuclear phagocyte system

○ B. Apoptosis of tissue mast cells and eosinophils

○ C. Clearance of intact drug molecules by kidneys

○ D. Endocytosis and degradation of mast cell-bound IgE

○ E. Regulatory T-cell–mediated cytotoxic T-cell suppression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- ✓ ○ A. Activation of the mononuclear phagocyte system (24%)
- ✗ ● B. Apoptosis of tissue mast cells and eosinophils (4%)
- ○ C. Clearance of intact drug molecules by kidneys (16%)
- ○ D. Endocytosis and degradation of mast cell-bound IgE (12%)
- ○ E. Regulatory T-cell–mediated cytotoxic T-cell suppression (42%)

Incorrect
Correct answer
A

24%
Answered correctly

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Time Spent

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Explanation

Chimeric monoclonal antibodies such as infliximab contain amino acid sequences from human and **non-human** (eg, mice) sources. These proteins are processed by antigen presenting cells, displayed on class II major histocompatibility complexes, and the nonhuman components are **recognized as foreign** by patrolling CD4 cells. The CD4 cells then stimulate activated B-cells to undergo somatic hypermutation and class switching, which generates plasma cells that secrete high-affinity **IgG antibodies against foreign components** of the drug

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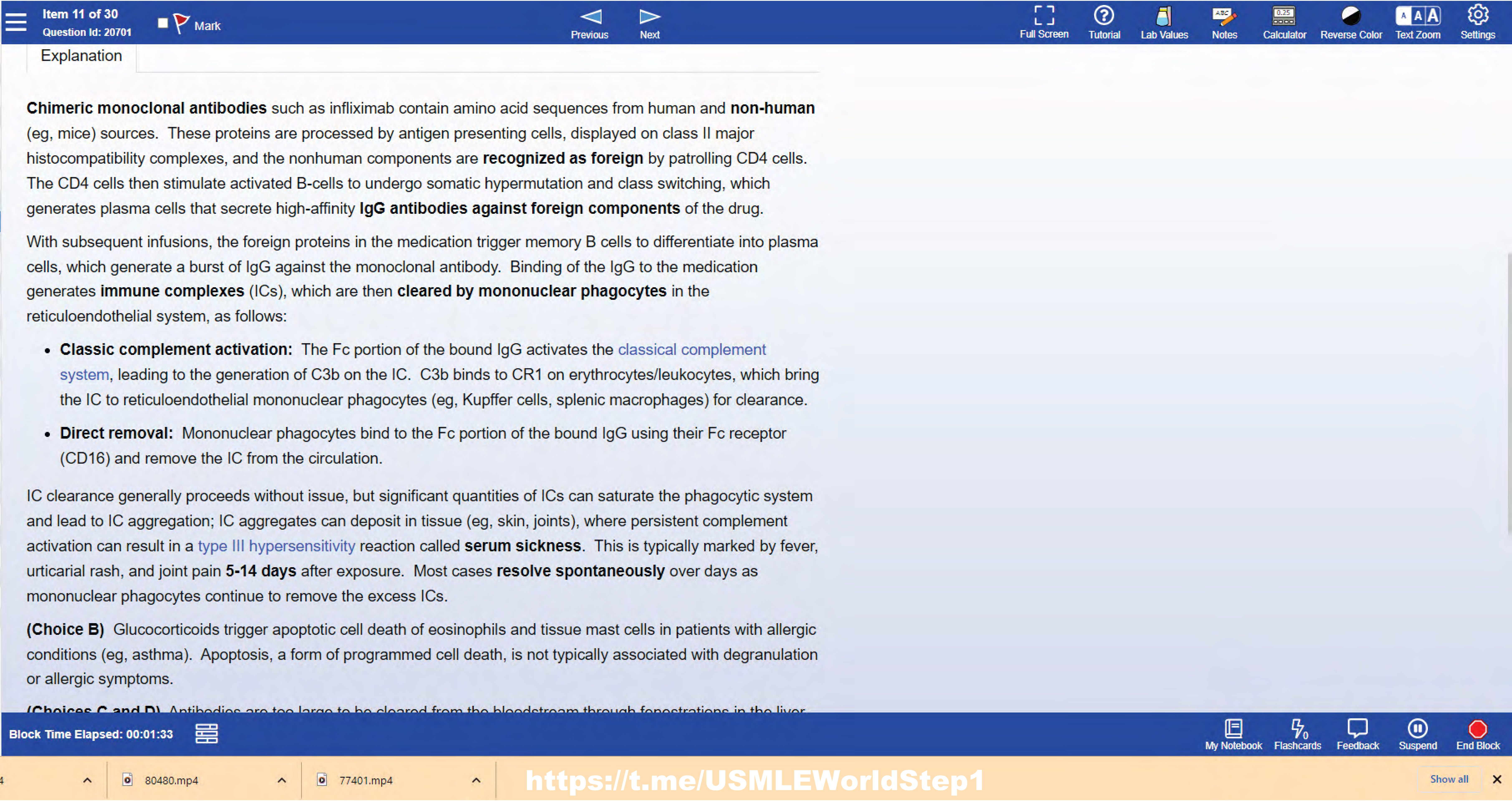
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Explanation

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With subsequent infusions, the foreign proteins in the medication trigger memory B cells to differentiate into plasma cells, which generate a burst of IgG against the monoclonal antibody. Binding of the IgG to the medication generates **immune complexes** (ICs), which are then **cleared by mononuclear phagocytes** in the reticuloendothelial system, as follows:

- **Classic complement activation:** The Fc portion of the bound IgG activates the classical complement system, leading to the generation of C3b on the IC. C3b binds to CR1 on erythrocytes/leukocytes, which bring the IC to reticuloendothelial mononuclear phagocytes (eg, Kupffer cells, splenic macrophages) for clearance.
- **Direct removal:** Mononuclear phagocytes bind to the Fc portion of the bound IgG using their Fc receptor (CD16) and remove the IC from the circulation.

IC clearance generally proceeds without issue, but significant quantities of ICs can saturate the phagocytic system and lead to IC aggregation; IC aggregates can deposit in tissue (eg, skin, joints), where persistent complement activation can result in a type III hypersensitivity reaction called **serum sickness**. This is typically marked by fever, urticarial rash, and joint pain **5-14 days** after exposure. Most cases **resolve spontaneously** over days as mononuclear phagocytes continue to remove the excess ICs.

(Choice B) Glucocorticoids trigger apoptotic cell death of eosinophils and tissue mast cells in patients with allergic conditions (eg, asthma). Apoptosis, a form of programmed cell death, is not typically associated with degranulation or allergic symptoms.

(Choices C and D) Antibodies are too large to be cleared from the bloodstream through fenestrations in the liver

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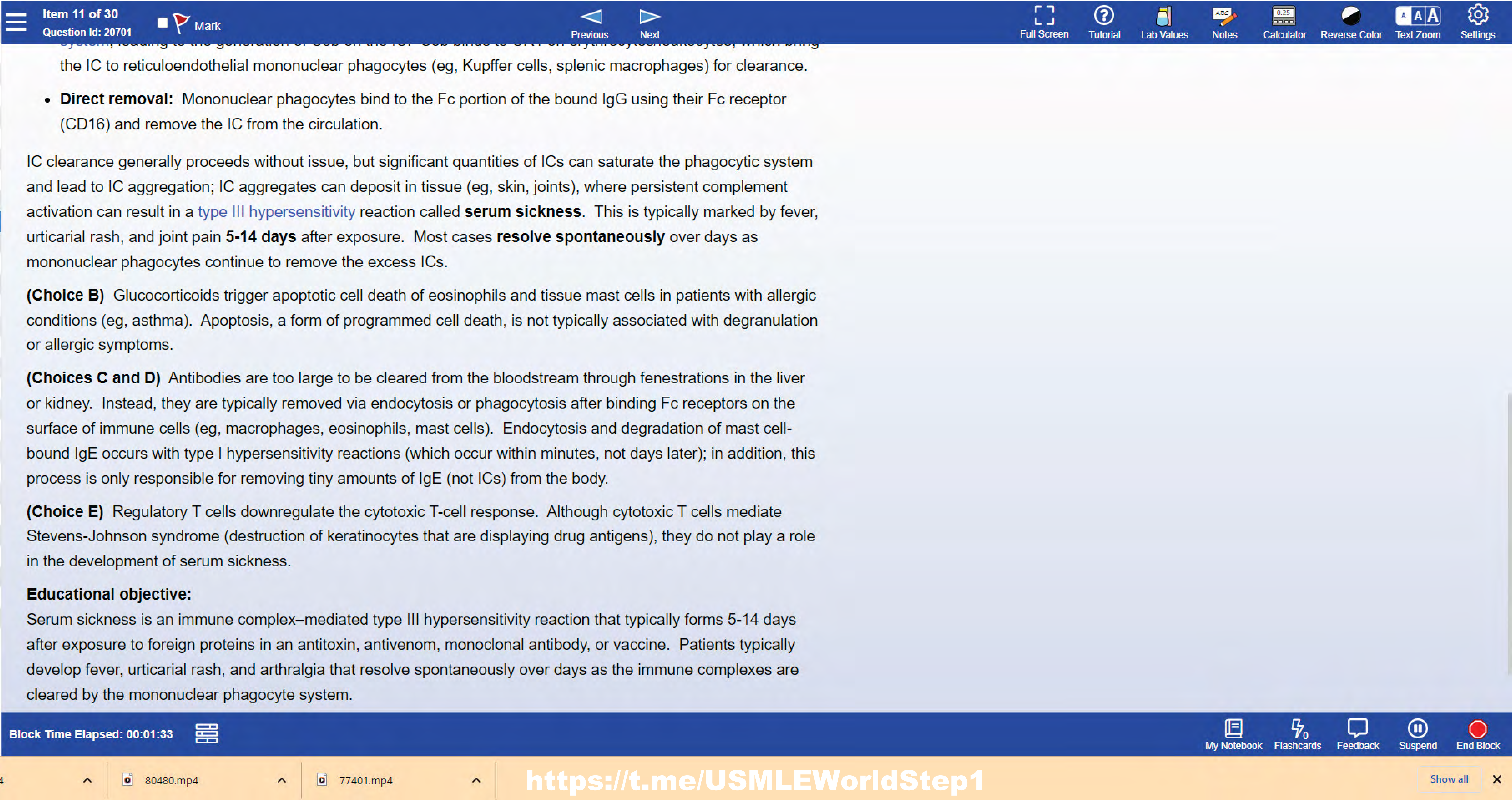

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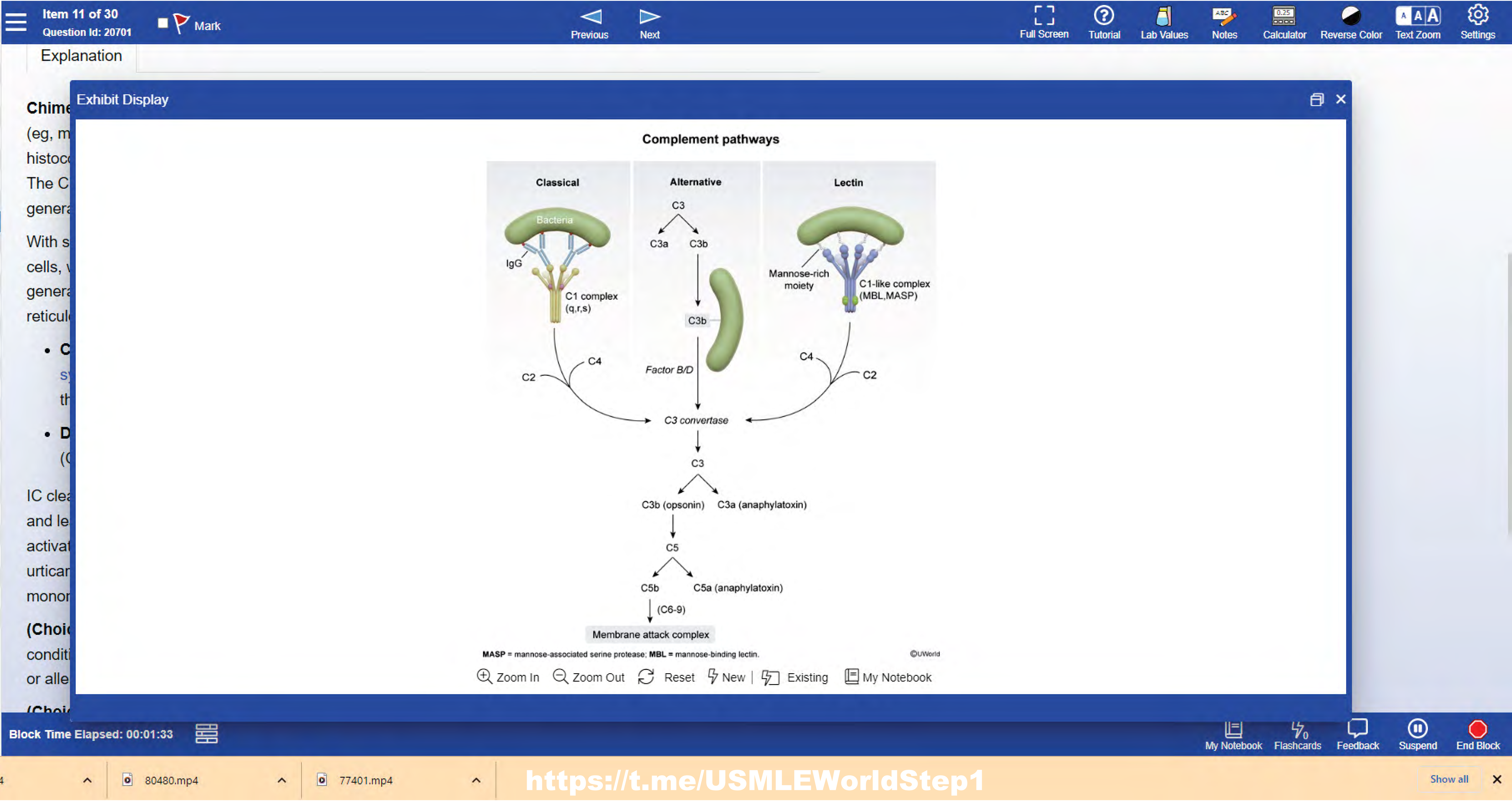
(Choice B) Glucocorticoids trigger apoptotic cell death of eosinophils and tissue mast cells in patients with allergic conditions (eg, asthma). Apoptosis, a form of programmed cell death, is not typically associated with degranulation or allergic symptoms.

(Choices C and D) Antibodies are too large to be cleared from the bloodstream through fenestrations in the liver or kidney. Instead, they are typically removed via endocytosis or phagocytosis after binding Fc receptors on the surface of immune cells (eg, macrophages, eosinophils, mast cells). Endocytosis and degradation of mast cell-bound IgE occurs with type I hypersensitivity reactions (which occur within minutes, not days later); in addition, this process is only responsible for removing tiny amounts of IgE (not ICs) from the body.

(Choice E) Regulatory T cells downregulate the cytotoxic T-cell response. Although cytotoxic T cells mediate Stevens-Johnson syndrome (destruction of keratinocytes that are displaying drug antigens), they do not play a role in the development of serum sickness.

Educational objective:
Serum sickness is an immune complex–mediated type III hypersensitivity reaction that typically forms 5-14 days after exposure to foreign proteins in an antitoxin, antivenom, monoclonal antibody, or vaccine. Patients typically develop fever, urticarial rash, and arthralgia that resolve spontaneously over days as the immune complexes are cleared by the mononuclear phagocyte system.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Classical
Bacteria
IgG
C1 complex (q,r,s)
C2
C4
Alternative
C3
C3a
C3b
C3b
Factor B/D
Lectin
Mannose-rich moiety
C1-like complex (MBL,MASP)
C4
C2
C3 convertase
C3
C3b (opsonin)
C3a (anaphylatoxin)
C5
C5b
C5a (anaphylatoxin)
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MASP = mannose-associated serine protease; **MBL** = mannose-binding lectin.

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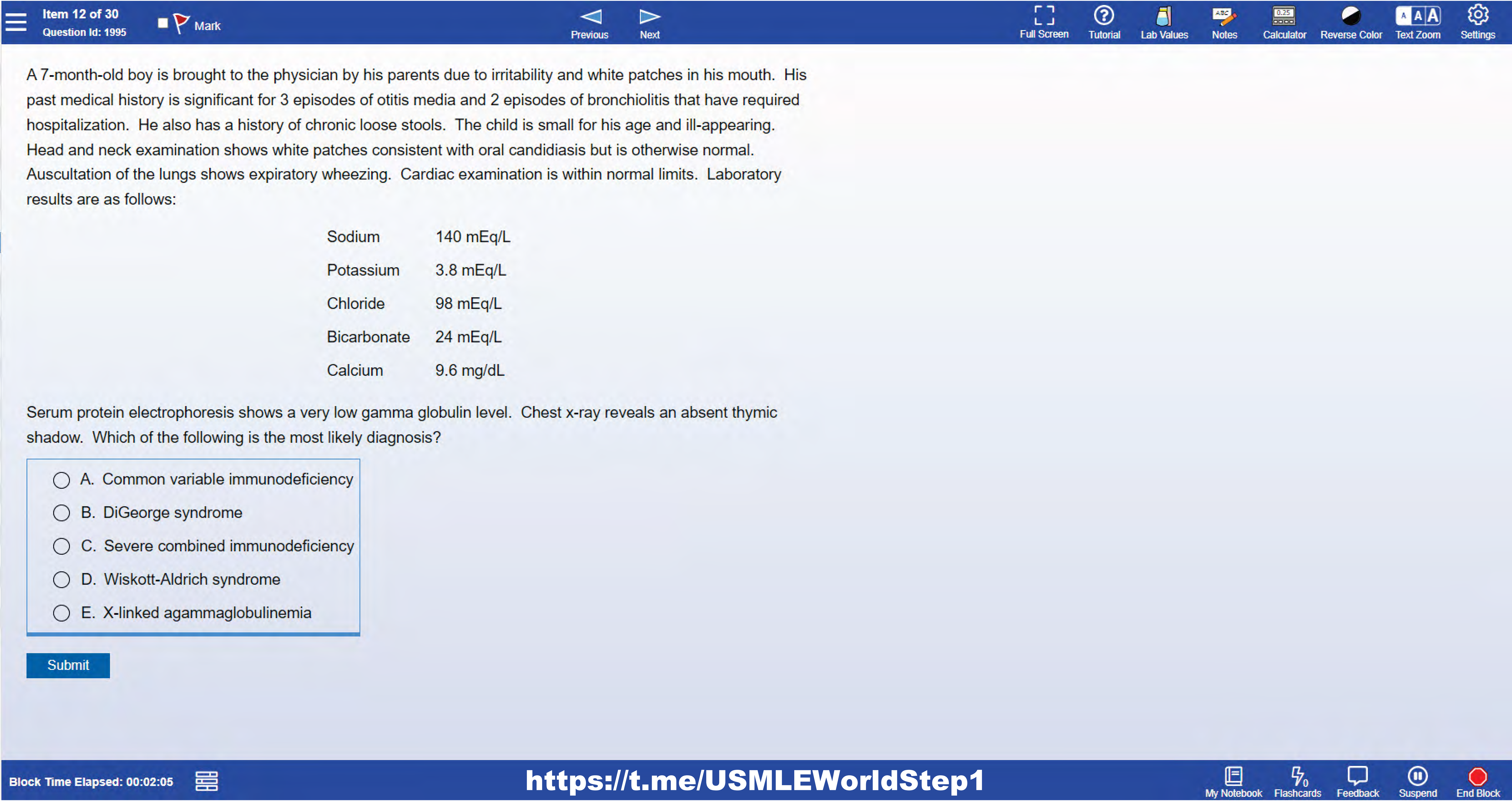
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A 7-month-old boy is brought to the physician by his parents due to irritability and white patches in his mouth. His past medical history is significant for 3 episodes of otitis media and 2 episodes of bronchiolitis that have required hospitalization. He also has a history of chronic loose stools. The child is small for his age and ill-appearing. Head and neck examination shows white patches consistent with oral candidiasis but is otherwise normal. Auscultation of the lungs shows expiratory wheezing. Cardiac examination is within normal limits. Laboratory results are as follows:

Sodium	140 mEq/L
Potassium	3.8 mEq/L
Chloride	98 mEq/L
Bicarbonate	24 mEq/L
Calcium	9.6 mg/dL

Serum protein electrophoresis shows a very low gamma globulin level. Chest x-ray reveals an absent thymic shadow. Which of the following is the most likely diagnosis?

- ○ A. Common variable immunodeficiency
- ○ B. DiGeorge syndrome
- ○ C. Severe combined immunodeficiency
- ○ D. Wiskott-Aldrich syndrome
- ○ E. X-linked agammaglobulinemia

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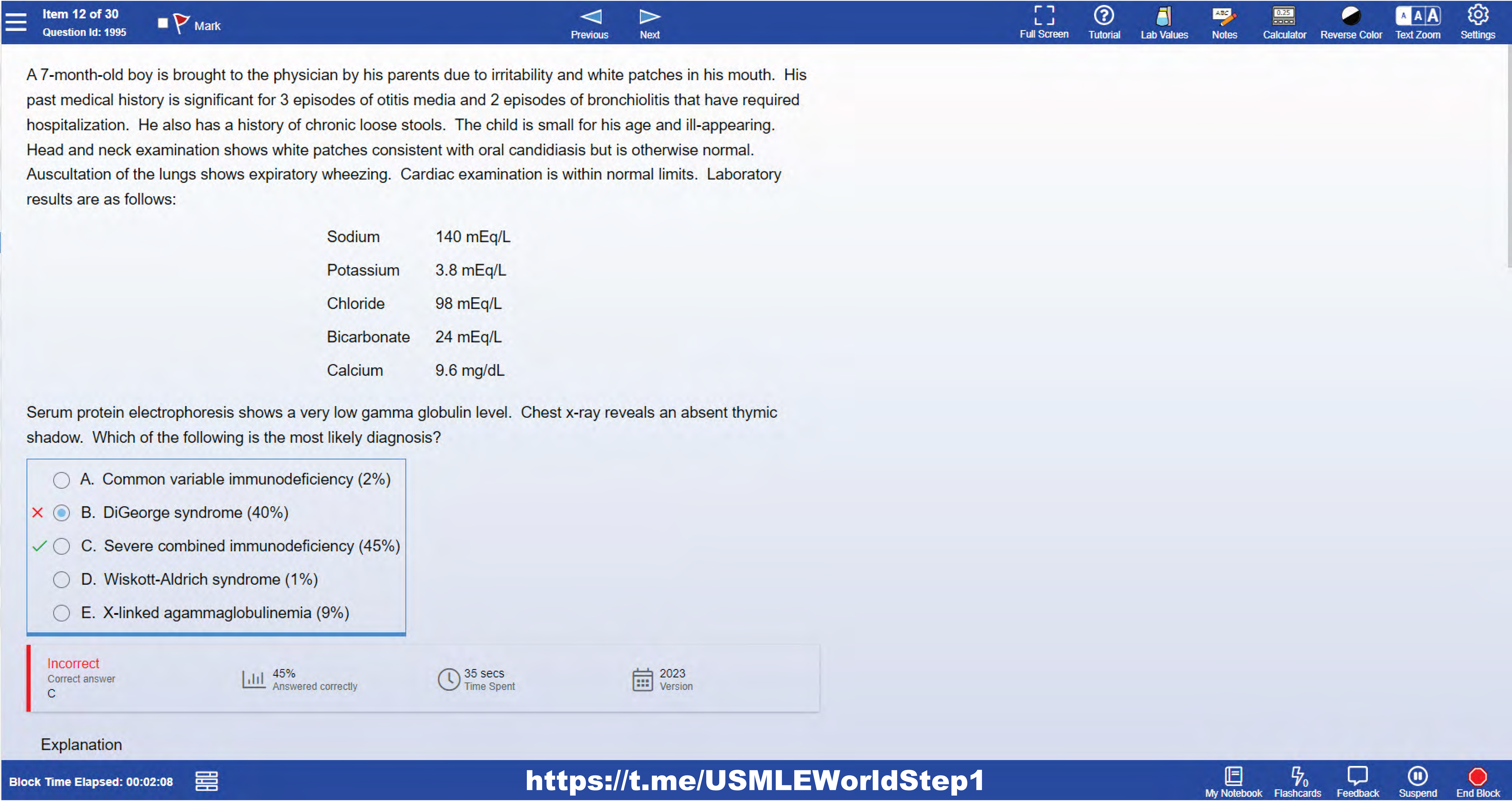
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Potassium	3.8 mEq/L
Chloride	98 mEq/L
Bicarbonate	24 mEq/L
Calcium	9.6 mg/dL

Serum protein electrophoresis shows a very low gamma globulin level. Chest x-ray reveals an absent thymic shadow. Which of the following is the most likely diagnosis?

○ A. Common variable immunodeficiency (2%)
✗ ● B. DiGeorge syndrome (40%)
✓ ○ C. Severe combined immunodeficiency (45%)
○ D. Wiskott-Aldrich syndrome (1%)
○ E. X-linked agammaglobulinemia (9%)

Incorrect
Correct answer
C

45%
Answered correctly

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Explanation

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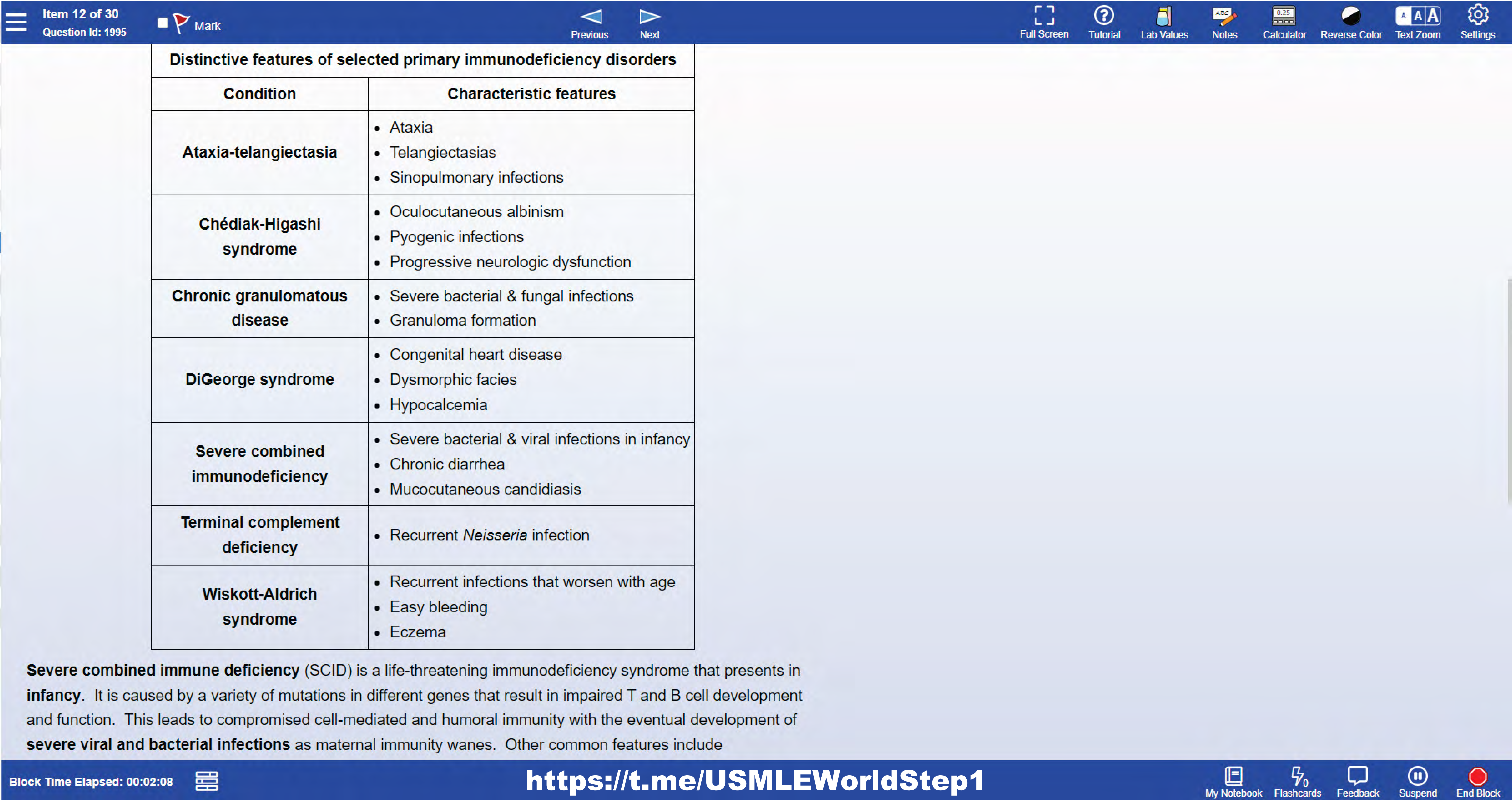
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Distinctive features of selected primary immunodeficiency disorders

Condition	Characteristic features
Ataxia-telangiectasia	• Ataxia • Telangiectasias • Sinopulmonary infections
Chédiak-Higashi syndrome	• Oculocutaneous albinism • Pyogenic infections • Progressive neurologic dysfunction
Chronic granulomatous disease	• Severe bacterial & fungal infections • Granuloma formation
DiGeorge syndrome	• Congenital heart disease • Dysmorphic facies • Hypocalcemia
Severe combined immunodeficiency	• Severe bacterial & viral infections in infancy • Chronic diarrhea • Mucocutaneous candidiasis
Terminal complement deficiency	• Recurrent *Neisseria* infection
Wiskott-Aldrich syndrome	• Recurrent infections that worsen with age • Easy bleeding • Eczema

Severe combined immune deficiency (SCID) is a life-threatening immunodeficiency syndrome that presents in **infancy**. It is caused by a variety of mutations in different genes that result in impaired T and B cell development and function. This leads to compromised cell-mediated and humoral immunity with the eventual development of **severe viral and bacterial infections** as maternal immunity wanes. Other common features include

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and function. This leads to compromised cell-mediated and humoral immunity with the eventual development of **severe viral and bacterial infections** as maternal immunity wanes. Other common features include mucocutaneous candidiasis, persistent diarrhea, and failure to thrive. Laboratory studies show very low or **absent CD3+ T cells** and **hypogammaglobulinemia**. Thymic hypoplasia or aplasia is another common finding in infants with SCID due to severe T cell deficiency.

(Choice A) Common variable immunodeficiency is a heterogenous condition caused by B and T cell dysfunction and characterized by hypogammaglobulinemia. It presents with recurrent infections in adults and children (after the neonatal period). While not entirely unaffected, cell-mediated immunity is not as impaired as in SCID and thymic aplasia is unlikely.

(Choice B) DiGeorge syndrome (DGS) classically presents with craniofacial abnormalities, conotruncal cardiac anomalies, hypoplastic thymus, and hypocalcemia resulting from parathyroid hypoplasia. Immunodeficiency can also occur and is related to the degree of thymic hypoplasia. Although complete DGS (<1% of cases) is a form of SCID, the absence of other characteristic findings makes DGS a less likely diagnosis.

(Choice D) In Wiskott-Aldrich syndrome, functioning of both T and B cells is impaired due to abnormal cytoskeletal functioning. Patients experience recurrent viral, bacterial, and fungal infections that generally worsen with age. However, Wiskott-Aldrich syndrome also typically causes bleeding due to thrombocytopenia and eczema.

(Choice E) X-linked (Bruton's) agammaglobulinemia is an immunodeficiency syndrome caused by insufficient production of mature B cells, which predisposes mainly to recurrent infections with encapsulated pyogenic bacteria (eg, *Streptococcus pneumoniae*, *Hemophilus influenzae* type B). The quantity and functioning of T cells is generally not affected, so an absent thymic shadow is unlikely.

Educational objective:

Severe combined immune deficiency is characterized by combined T and B cell dysfunction. It is a life-threatening condition that presents in infancy with severe bacterial and viral infections; mucocutaneous candidiasis; persistent diarrhea; and failure to thrive. Laboratory findings include absent T cells and hypogammaglobulinemia. The thymic shadow is not usually present due to severe T cell deficiency.

References

- Educational paper. The expanding clinical and immunological spectrum of severe combined immunodeficiency.

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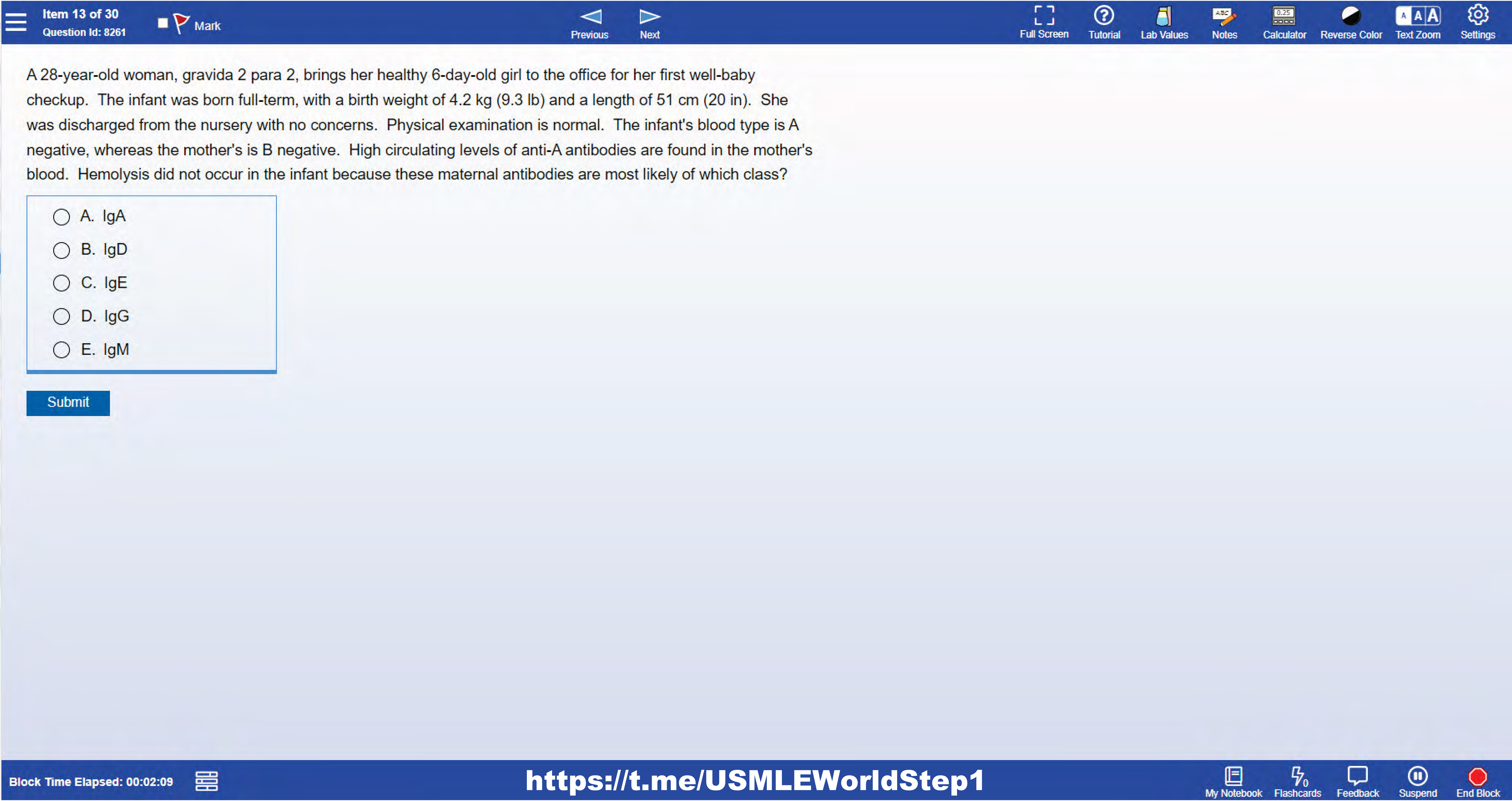
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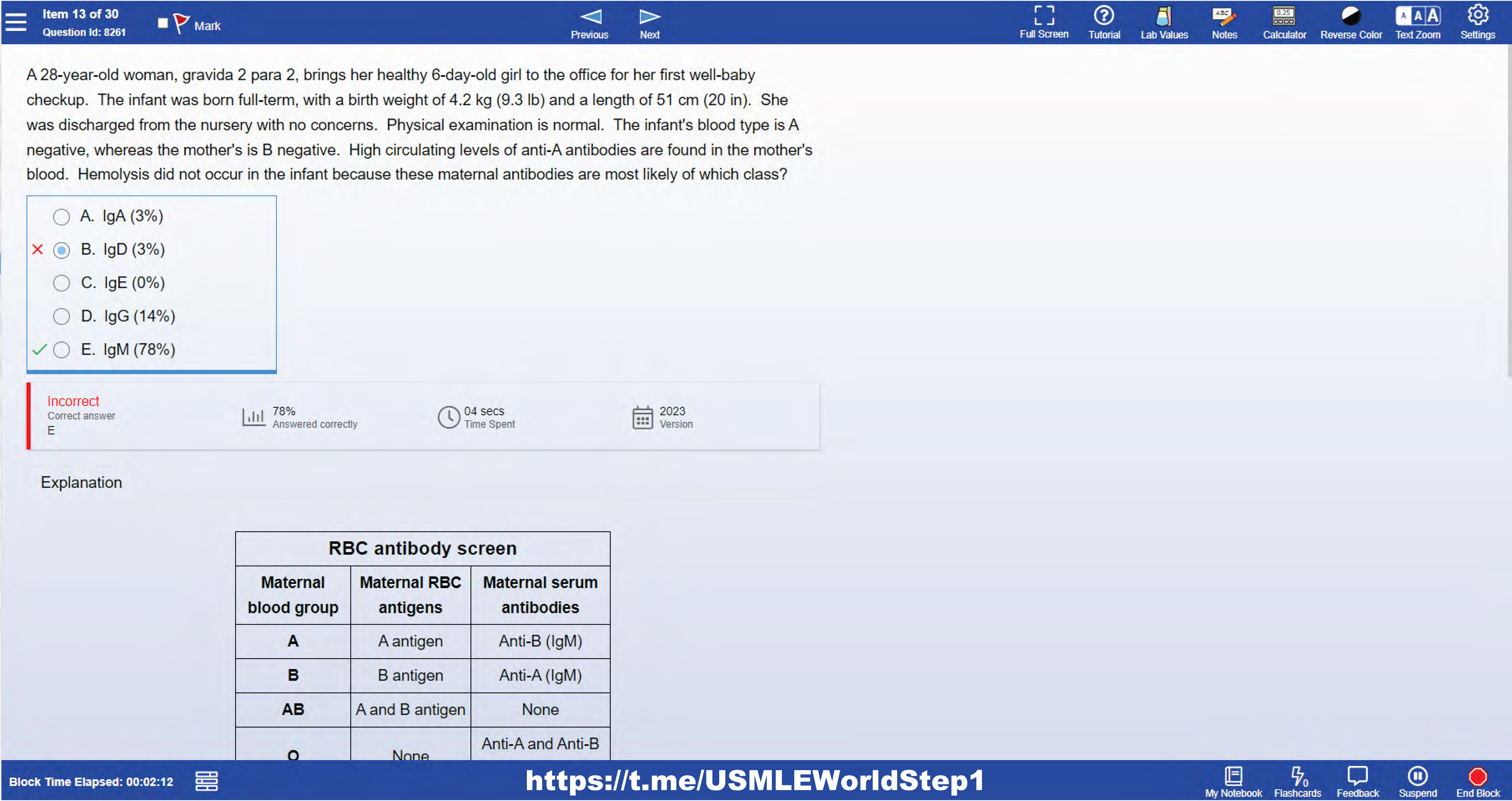
A 28-year-old woman, gravida 2 para 2, brings her healthy 6-day-old girl to the office for her first well-baby checkup. The infant was born full-term, with a birth weight of 4.2 kg (9.3 lb) and a length of 51 cm (20 in). She was discharged from the nursery with no concerns. Physical examination is normal. The infant's blood type is A negative, whereas the mother's is B negative. High circulating levels of anti-A antibodies are found in the mother's blood. Hemolysis did not occur in the infant because these maternal antibodies are most likely of which class?

○ A. IgA
○ B. IgD
○ C. IgE
○ D. IgG
○ E. IgM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○ A. IgA (3%)
✗ ● B. IgD (3%)
○ C. IgE (0%)
○ D. IgG (14%)
✓ ○ E. IgM (78%)

Incorrect
Correct answer
E

78%
Answered correctly

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Explanation

RBC antibody screen		
Maternal blood group	**Maternal RBC antigens**	**Maternal serum antibodies**
A	A antigen	Anti-B (IgM)
B	B antigen	Anti-A (IgM)
AB	A and B antigen	None
O	None	Anti-A and Anti-B

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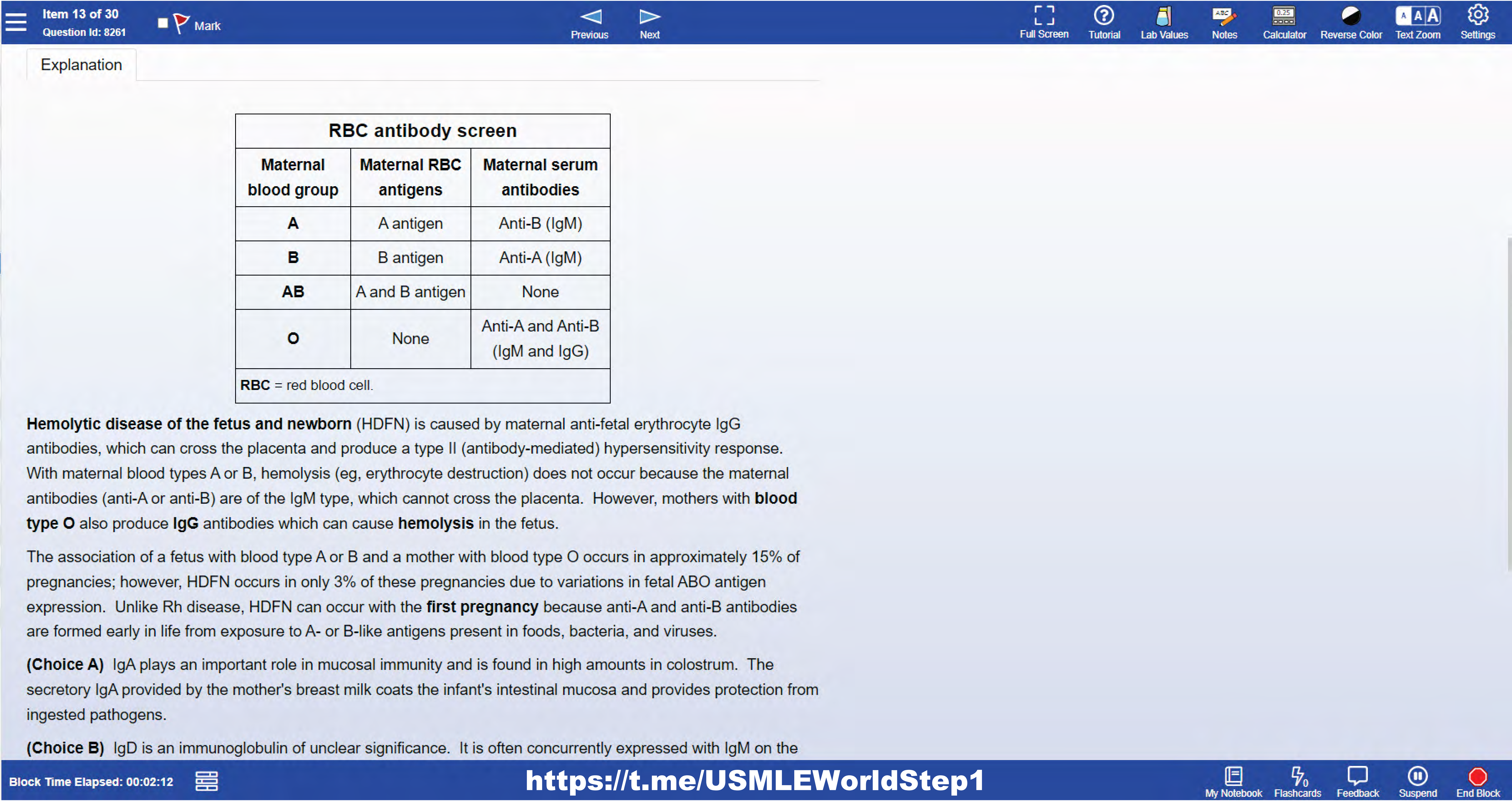
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RBC antibody screen

Maternal blood group	Maternal RBC antigens	Maternal serum antibodies
A	A antigen	Anti-B (IgM)
B	B antigen	Anti-A (IgM)
AB	A and B antigen	None
O	None	Anti-A and Anti-B (IgM and IgG)

RBC = red blood cell.

Hemolytic disease of the fetus and newborn (HDFN) is caused by maternal anti-fetal erythrocyte IgG antibodies, which can cross the placenta and produce a type II (antibody-mediated) hypersensitivity response. With maternal blood types A or B, hemolysis (eg, erythrocyte destruction) does not occur because the maternal antibodies (anti-A or anti-B) are of the IgM type, which cannot cross the placenta. However, mothers with **blood type O** also produce **IgG** antibodies which can cause **hemolysis** in the fetus.

The association of a fetus with blood type A or B and a mother with blood type O occurs in approximately 15% of pregnancies; however, HDFN occurs in only 3% of these pregnancies due to variations in fetal ABO antigen expression. Unlike Rh disease, HDFN can occur with the **first pregnancy** because anti-A and anti-B antibodies are formed early in life from exposure to A- or B-like antigens present in foods, bacteria, and viruses.

(Choice A) IgA plays an important role in mucosal immunity and is found in high amounts in colostrum. The secretory IgA provided by the mother's breast milk coats the infant's intestinal mucosa and provides protection from ingested pathogens.

(Choice B) IgD is an immunoglobulin of unclear significance. It is often concurrently expressed with IgM on the

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RBC = red blood cell.

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The association of a fetus with blood type A or B and a mother with blood type O occurs in approximately 15% of pregnancies; however, HDFN occurs in only 3% of these pregnancies due to variations in fetal ABO antigen expression. Unlike Rh disease, HDFN can occur with the **first pregnancy** because anti-A and anti-B antibodies are formed early in life from exposure to A- or B-like antigens present in foods, bacteria, and viruses.

(Choice A) IgA plays an important role in mucosal immunity and is found in high amounts in colostrum. The secretory IgA provided by the mother's breast milk coats the infant's intestinal mucosa and provides protection from ingested pathogens.

(Choice B) IgD is an immunoglobulin of unclear significance. It is often concurrently expressed with IgM on the membranes of B lymphocytes and is believed to act as a cell surface antigen receptor for those cells.

(Choice C) IgE is the immunoglobulin most notably responsible for atopic diseases such as asthma, atopic dermatitis, and allergic rhinitis. It also plays a role in defense against helminth parasites.

(Choice D) IgG crosses the placenta and remains circulating in the bloodstream of infants, providing them with passive immunity for up to 6 months.

Educational objective:

With maternal blood types A or B, hemolytic disease of the fetus and newborn very rarely occurs because maternal antibodies (anti-A or anti-B) are of the IgM type and cannot cross the placenta. In contrast, mothers with blood type O also produce IgG antibodies (anti-A and anti-B), which can cross the placenta and cause fetal hemolysis.

References

- Haemolytic disease of fetus and newborn.

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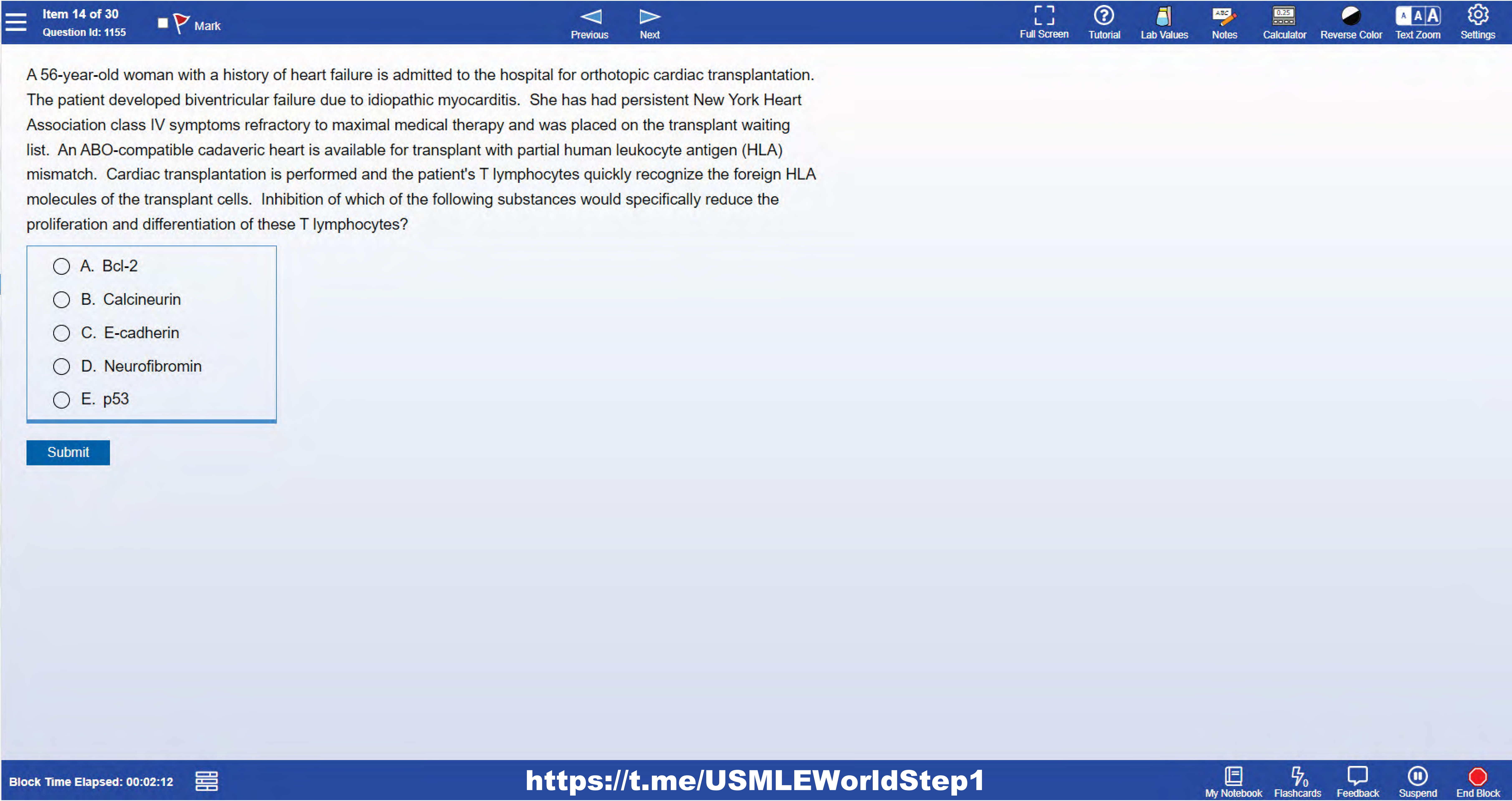
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A 56-year-old woman with a history of heart failure is admitted to the hospital for orthotopic cardiac transplantation. The patient developed biventricular failure due to idiopathic myocarditis. She has had persistent New York Heart Association class IV symptoms refractory to maximal medical therapy and was placed on the transplant waiting list. An ABO-compatible cadaveric heart is available for transplant with partial human leukocyte antigen (HLA) mismatch. Cardiac transplantation is performed and the patient's T lymphocytes quickly recognize the foreign HLA molecules of the transplant cells. Inhibition of which of the following substances would specifically reduce the proliferation and differentiation of these T lymphocytes?

○ A. Bcl-2
○ B. Calcineurin
○ C. E-cadherin
○ D. Neurofibromin
○ E. p53

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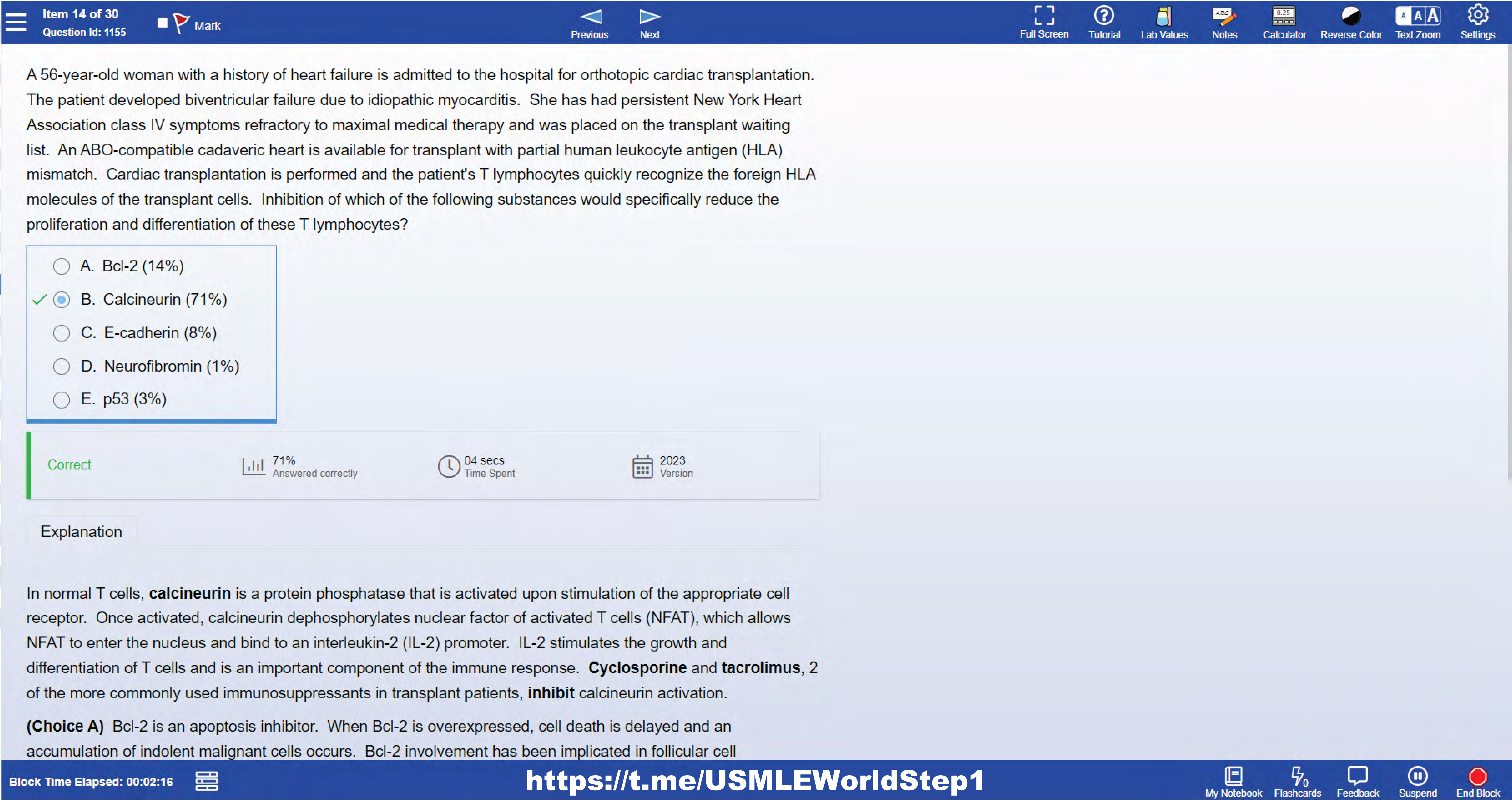
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○ A. Bcl-2 (14%)
✓ ● B. Calcineurin (71%)
○ C. E-cadherin (8%)
○ D. Neurofibromin (1%)
○ E. p53 (3%)

Correct | 71% Answered correctly | 04 secs Time Spent | 2023 Version

Explanation

In normal T cells, **calcineurin** is a protein phosphatase that is activated upon stimulation of the appropriate cell receptor. Once activated, calcineurin dephosphorylates nuclear factor of activated T cells (NFAT), which allows NFAT to enter the nucleus and bind to an interleukin-2 (IL-2) promoter. IL-2 stimulates the growth and differentiation of T cells and is an important component of the immune response. **Cyclosporine** and **tacrolimus**, 2 of the more commonly used immunosuppressants in transplant patients, **inhibit** calcineurin activation.

(Choice A) Bcl-2 is an apoptosis inhibitor. When Bcl-2 is overexpressed, cell death is delayed and an accumulation of indolent malignant cells occurs. Bcl-2 involvement has been implicated in follicular cell

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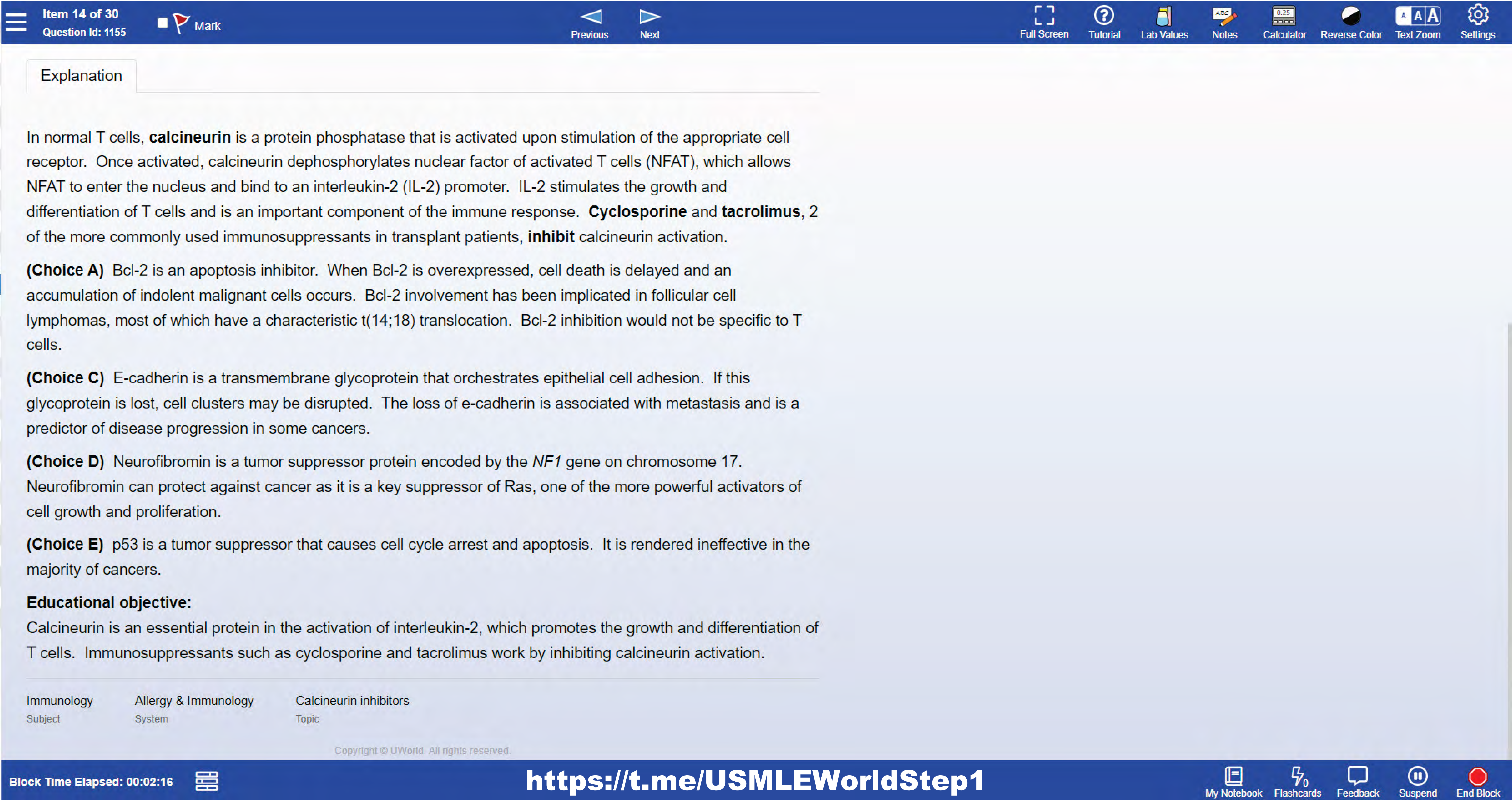
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(Choice A) Bcl-2 is an apoptosis inhibitor. When Bcl-2 is overexpressed, cell death is delayed and an accumulation of indolent malignant cells occurs. Bcl-2 involvement has been implicated in follicular cell lymphomas, most of which have a characteristic t(14;18) translocation. Bcl-2 inhibition would not be specific to T cells.

(Choice C) E-cadherin is a transmembrane glycoprotein that orchestrates epithelial cell adhesion. If this glycoprotein is lost, cell clusters may be disrupted. The loss of e-cadherin is associated with metastasis and is a predictor of disease progression in some cancers.

(Choice D) Neurofibromin is a tumor suppressor protein encoded by the *NF1* gene on chromosome 17. Neurofibromin can protect against cancer as it is a key suppressor of Ras, one of the more powerful activators of cell growth and proliferation.

(Choice E) p53 is a tumor suppressor that causes cell cycle arrest and apoptosis. It is rendered ineffective in the majority of cancers.

Educational objective:
Calcineurin is an essential protein in the activation of interleukin-2, which promotes the growth and differentiation of T cells. Immunosuppressants such as cyclosporine and tacrolimus work by inhibiting calcineurin activation.

Immunology	Allergy & Immunology	Calcineurin inhibitors
Subject	System	Topic

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Immunoglobulins of different classes have different structures. Some immunoglobulins have long hinge regions between the Fab and Fc regions, whereas others lack the hinge region, as shown in the image below:

The hinge region provides movement flexibility to the Fab regions. This is most likely to affect which of the following immunoglobulin properties?

○ A. Affinity to antigen
○ B. Antibody polymerization
○ C. Avidity to antigen
○ D. Effector cell interaction
○ E. Effector cell specificity

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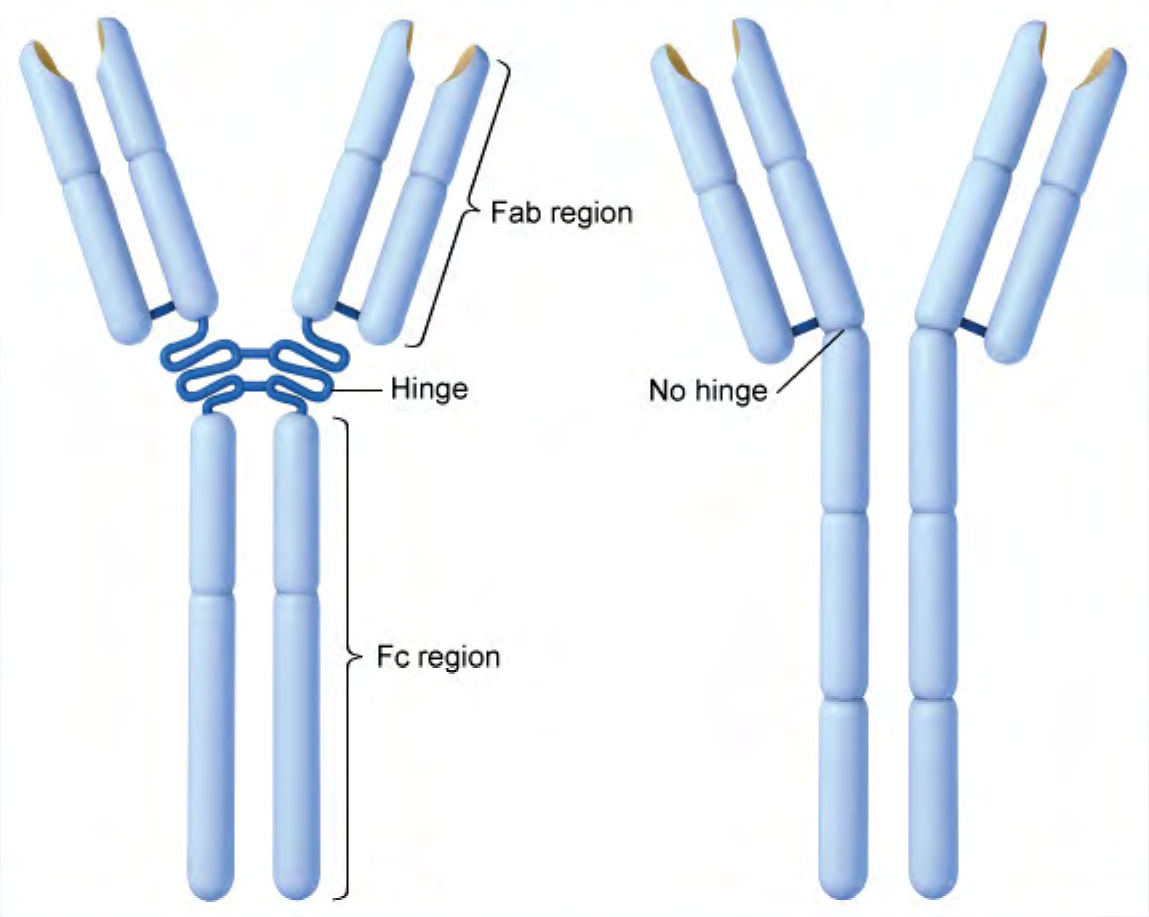

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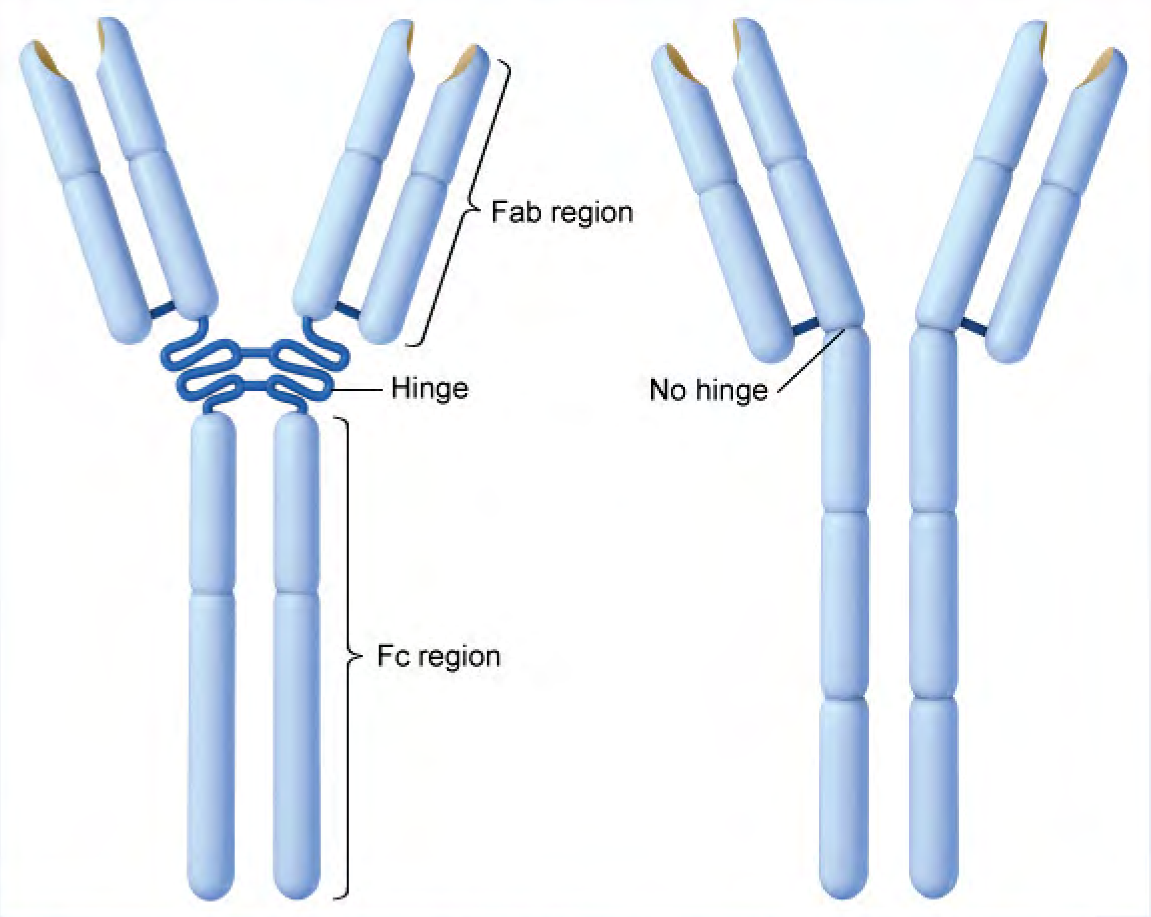

The hinge region provides movement flexibility to the Fab regions. This is most likely to affect which of the following immunoglobulin properties?

○ A. Affinity to antigen (19%)

✗ ● B. Antibody polymerization (19%)

✓ ○ C. Avidity to antigen (34%)

○ D. Effector cell interaction (22%)

○ E. Effector cell specificity (4%)

Incorrect
Correct answer
C

34%
Answered correctly

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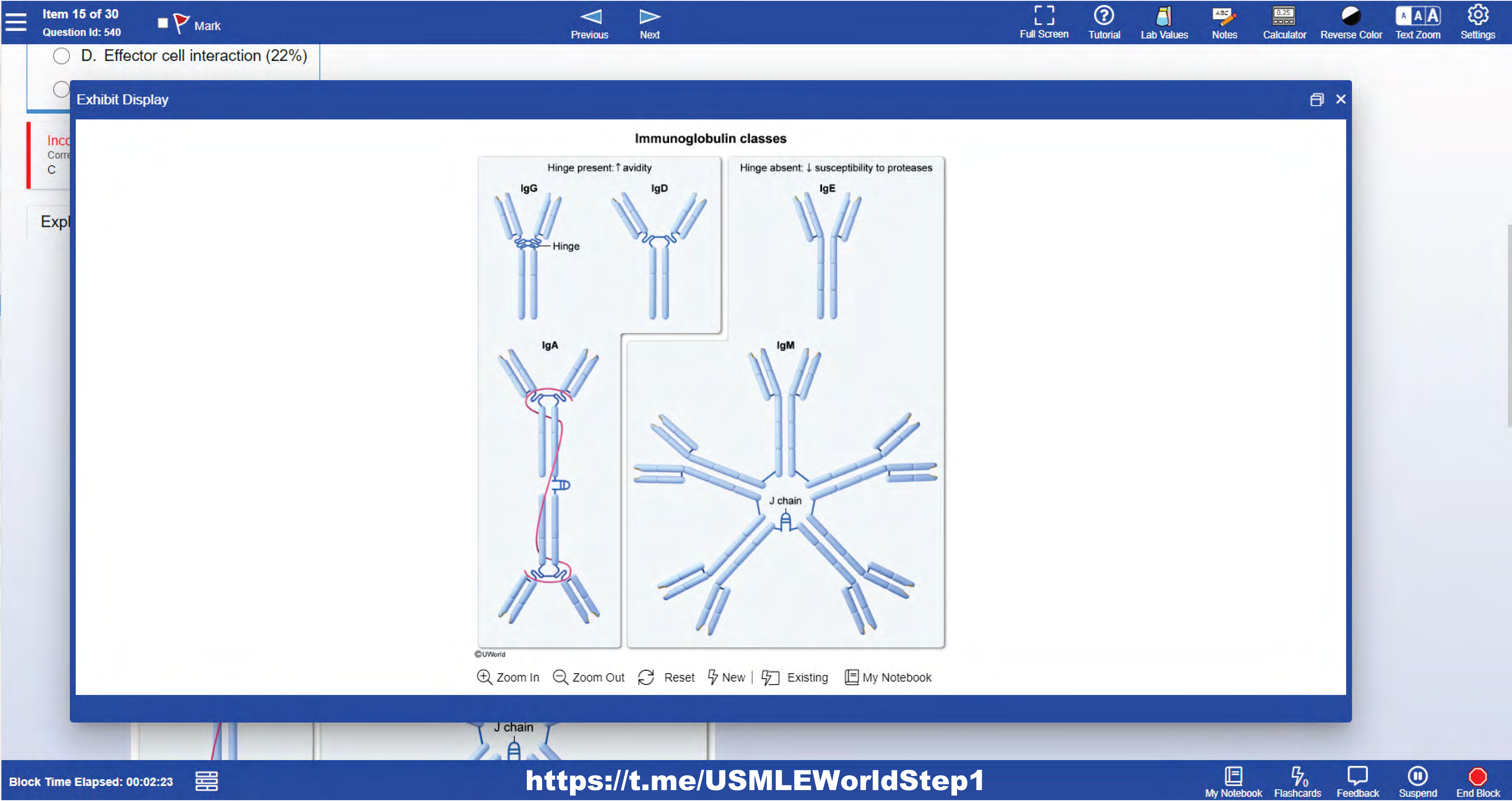
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○ D. Effector cell interaction (22%)

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Immunoglobulin classes

Hinge present: ↑ avidity
IgG
Hinge
IgD
Hinge absent: ↓ susceptibility to proteases
IgE
IgA
IgM
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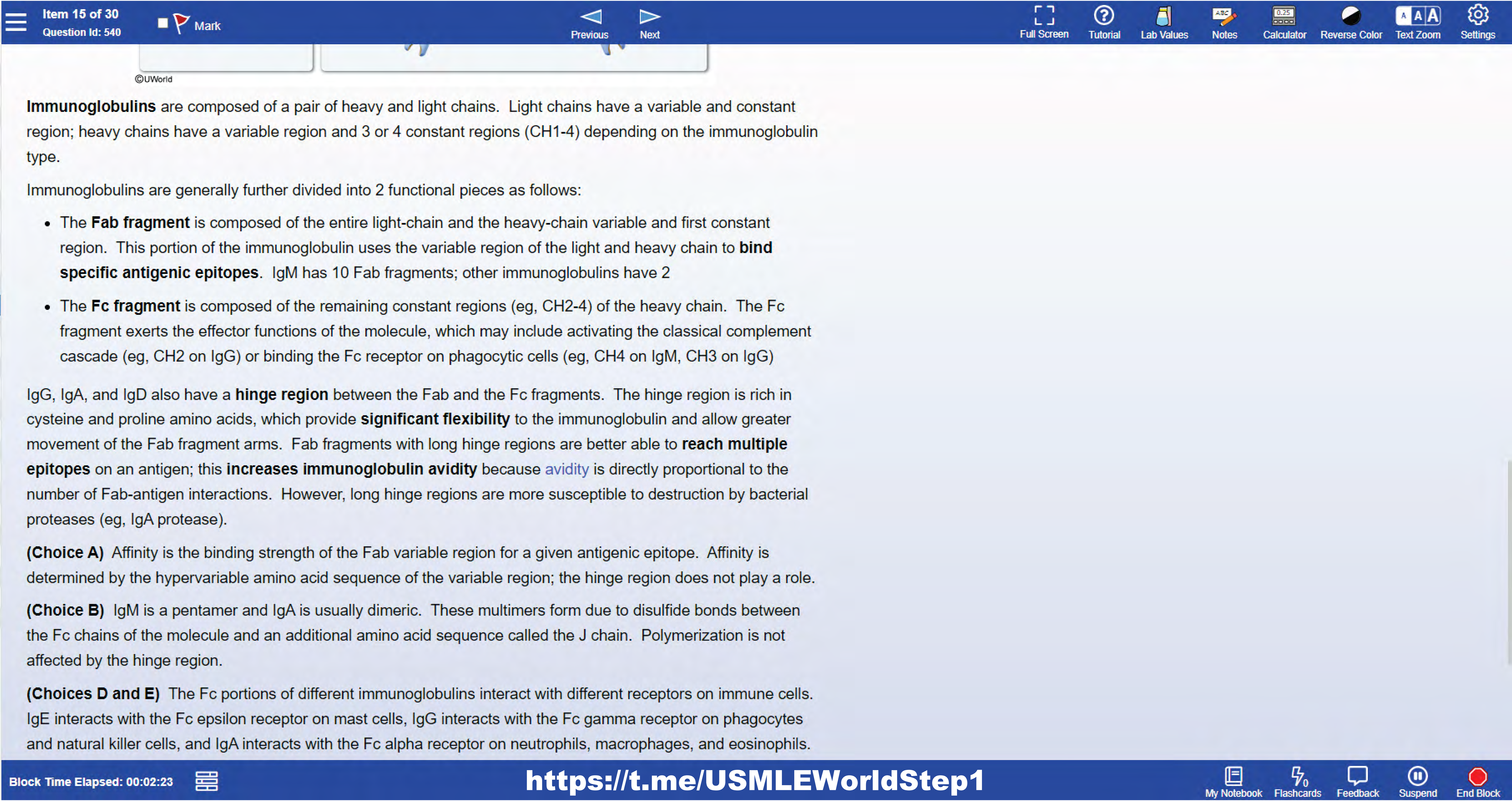

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Immunoglobulins are composed of a pair of heavy and light chains. Light chains have a variable and constant region; heavy chains have a variable region and 3 or 4 constant regions (CH1-4) depending on the immunoglobulin type.

Immunoglobulins are generally further divided into 2 functional pieces as follows:

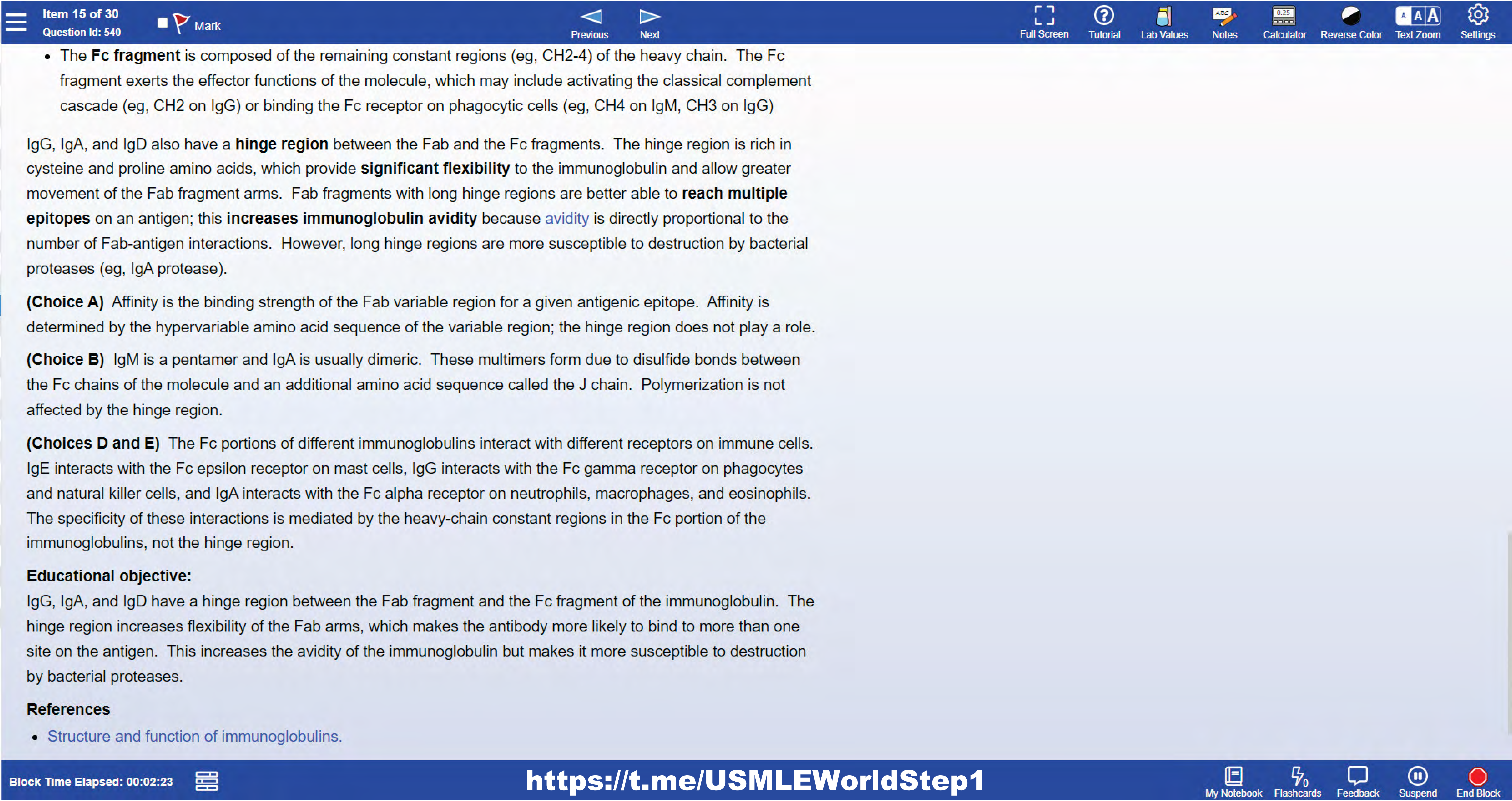
- The **Fab fragment** is composed of the entire light-chain and the heavy-chain variable and first constant region. This portion of the immunoglobulin uses the variable region of the light and heavy chain to **bind specific antigenic epitopes**. IgM has 10 Fab fragments; other immunoglobulins have 2
- The **Fc fragment** is composed of the remaining constant regions (eg, CH2-4) of the heavy chain. The Fc fragment exerts the effector functions of the molecule, which may include activating the classical complement cascade (eg, CH2 on IgG) or binding the Fc receptor on phagocytic cells (eg, CH4 on IgM, CH3 on IgG)

IgG, IgA, and IgD also have a **hinge region** between the Fab and the Fc fragments. The hinge region is rich in cysteine and proline amino acids, which provide **significant flexibility** to the immunoglobulin and allow greater movement of the Fab fragment arms. Fab fragments with long hinge regions are better able to **reach multiple epitopes** on an antigen; this **increases immunoglobulin avidity** because avidity is directly proportional to the number of Fab-antigen interactions. However, long hinge regions are more susceptible to destruction by bacterial proteases (eg, IgA protease).

(Choice A) Affinity is the binding strength of the Fab variable region for a given antigenic epitope. Affinity is determined by the hypervariable amino acid sequence of the variable region; the hinge region does not play a role.

(Choice B) IgM is a pentamer and IgA is usually dimeric. These multimers form due to disulfide bonds between the Fc chains of the molecule and an additional amino acid sequence called the J chain. Polymerization is not affected by the hinge region.

(Choices D and E) The Fc portions of different immunoglobulins interact with different receptors on immune cells. IgE interacts with the Fc epsilon receptor on mast cells, IgG interacts with the Fc gamma receptor on phagocytes and natural killer cells, and IgA interacts with the Fc alpha receptor on neutrophils, macrophages, and eosinophils.



- The **Fc fragment** is composed of the remaining constant regions (eg, CH2-4) of the heavy chain. The Fc fragment exerts the effector functions of the molecule, which may include activating the classical complement cascade (eg, CH2 on IgG) or binding the Fc receptor on phagocytic cells (eg, CH4 on IgM, CH3 on IgG)

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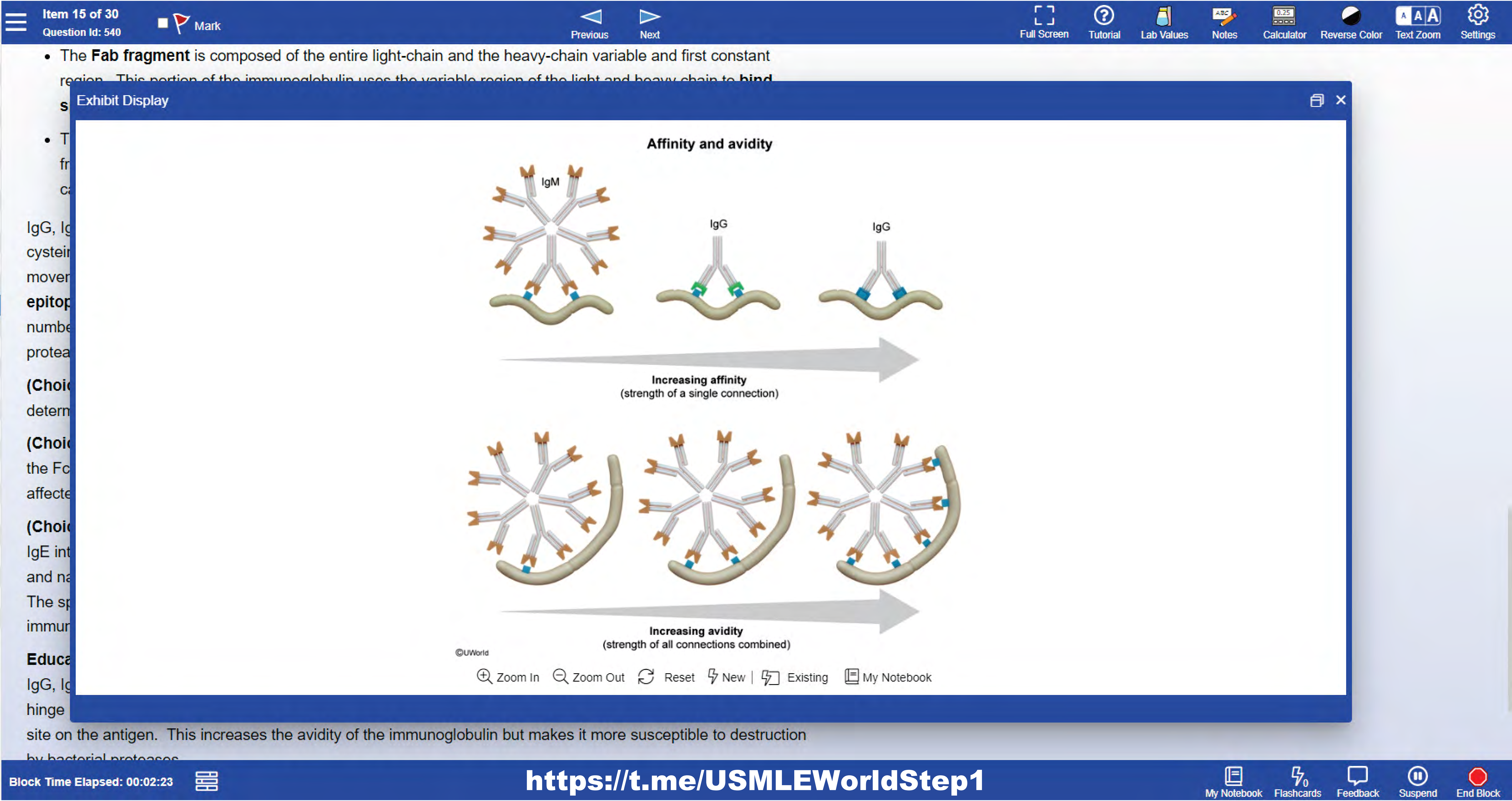
Educational objective:

IgG, IgA, and IgD have a hinge region between the Fab fragment and the Fc fragment of the immunoglobulin. The hinge region increases flexibility of the Fab arms, which makes the antibody more likely to bind to more than one site on the antigen. This increases the avidity of the immunoglobulin but makes it more susceptible to destruction by bacterial proteases.

References

- Structure and function of immunoglobulins.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- The **Fab fragment** is composed of the entire light-chain and the heavy-chain variable and first constant region. This portion of the immunoglobulin uses the variable region of the light and heavy chain to **bind** **s**
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site on the antigen. This increases the avidity of the immunoglobulin but makes it more susceptible to destruction by bacterial proteases.

Exhibit Display

Affinity and avidity

IgM
IgG
IgG
Increasing affinity
(strength of a single connection)
Increasing avidity
(strength of all connections combined)
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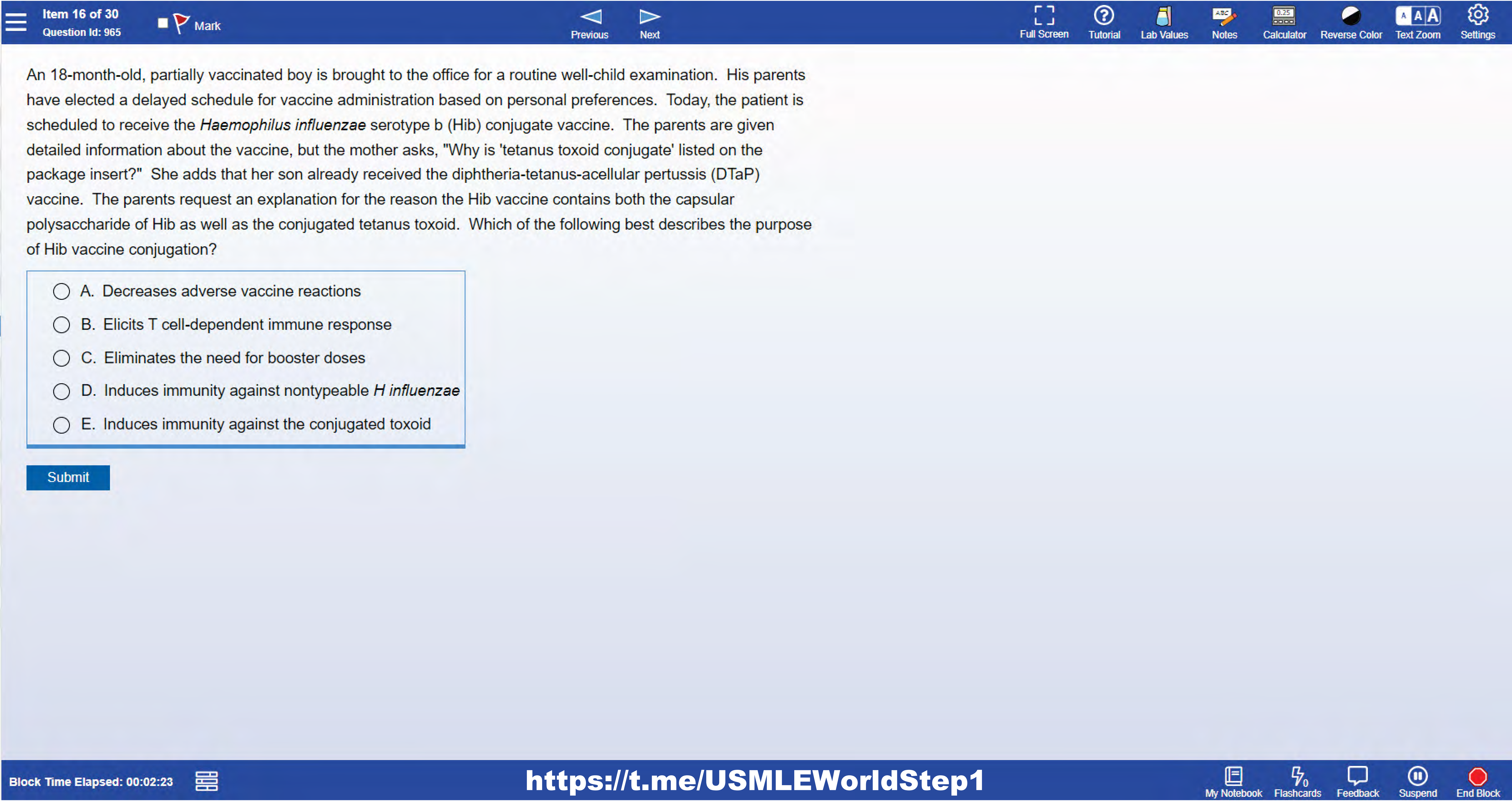
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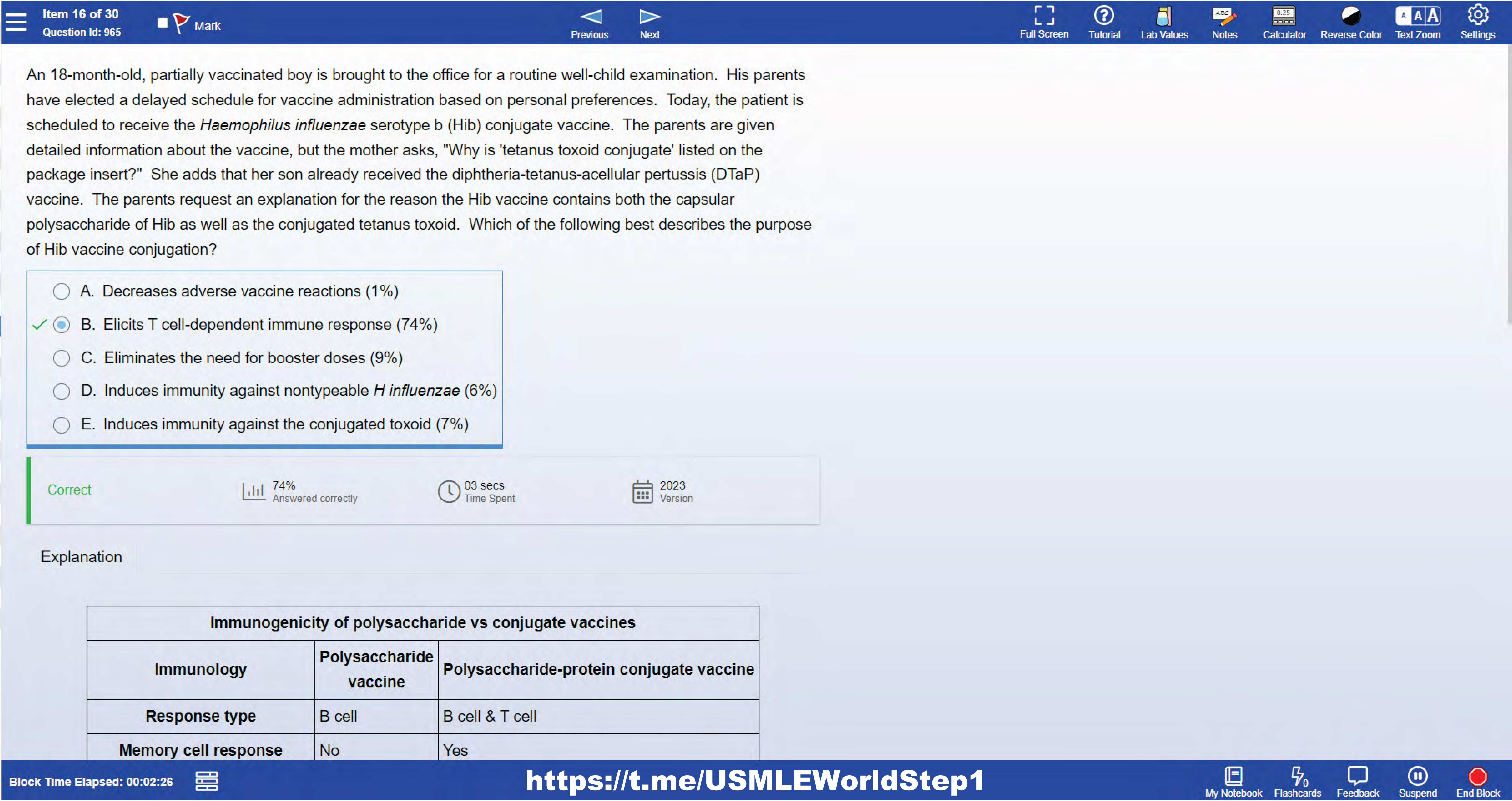
An 18-month-old, partially vaccinated boy is brought to the office for a routine well-child examination. His parents have elected a delayed schedule for vaccine administration based on personal preferences. Today, the patient is scheduled to receive the *Haemophilus influenzae* serotype b (Hib) conjugate vaccine. The parents are given detailed information about the vaccine, but the mother asks, "Why is 'tetanus toxoid conjugate' listed on the package insert?" She adds that her son already received the diphtheria-tetanus-acellular pertussis (DTaP) vaccine. The parents request an explanation for the reason the Hib vaccine contains both the capsular polysaccharide of Hib as well as the conjugated tetanus toxoid. Which of the following best describes the purpose of Hib vaccine conjugation?

○ A. Decreases adverse vaccine reactions
○ B. Elicits T cell-dependent immune response
○ C. Eliminates the need for booster doses
○ D. Induces immunity against nontypeable *H influenzae*
○ E. Induces immunity against the conjugated toxoid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○ A. Decreases adverse vaccine reactions (1%)

✓ ● B. Elicits T cell-dependent immune response (74%)

○ C. Eliminates the need for booster doses (9%)

○ D. Induces immunity against nontypeable *H influenzae* (6%)

○ E. Induces immunity against the conjugated toxoid (7%)

Correct

74% Answered correctly

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Explanation

Immunogenicity of polysaccharide vs conjugate vaccines		
Immunology	**Polysaccharide vaccine**	**Polysaccharide-protein conjugate vaccine**
Response type	B cell	B cell & T cell
Memory cell response	No	Yes

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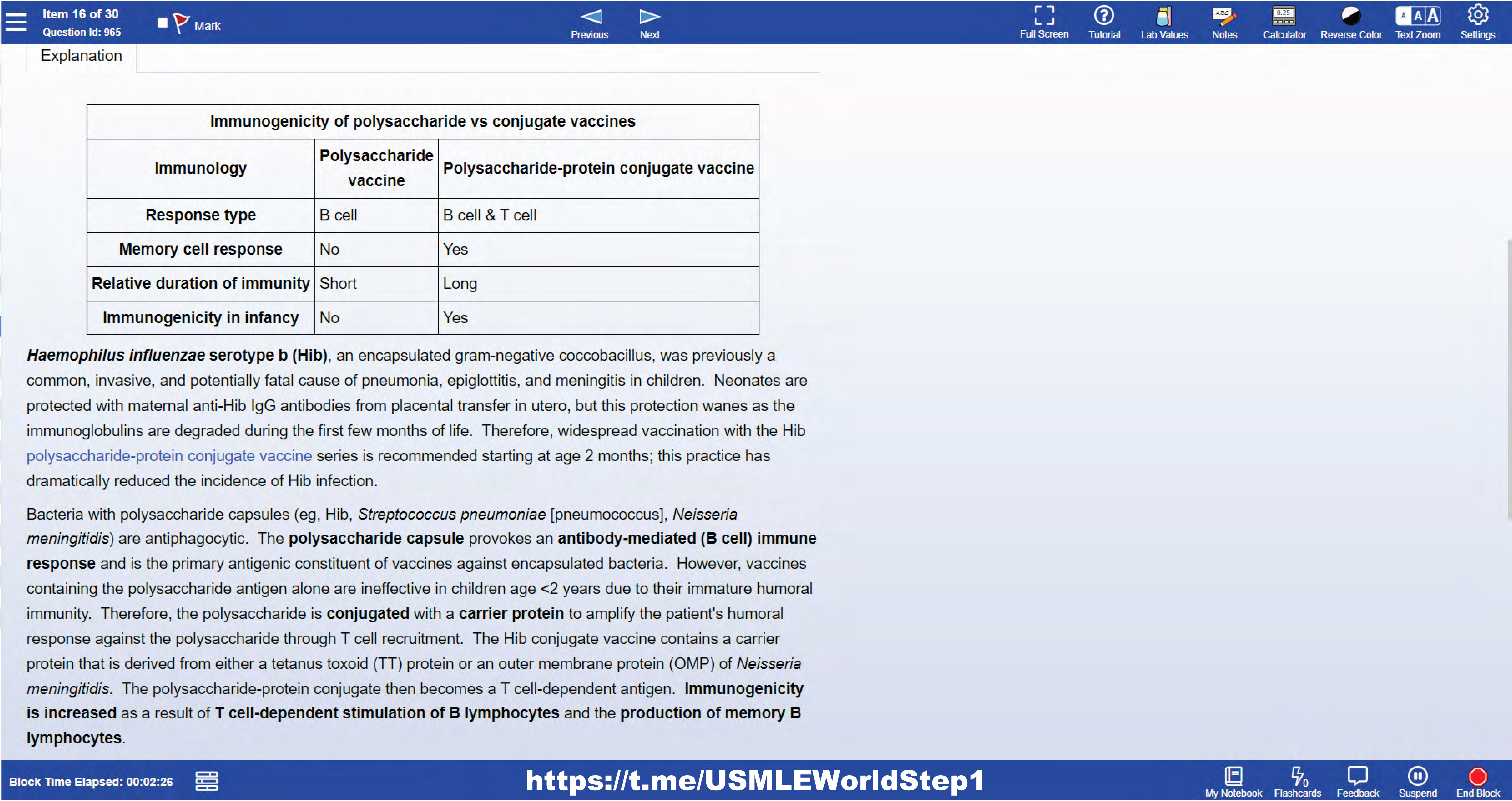
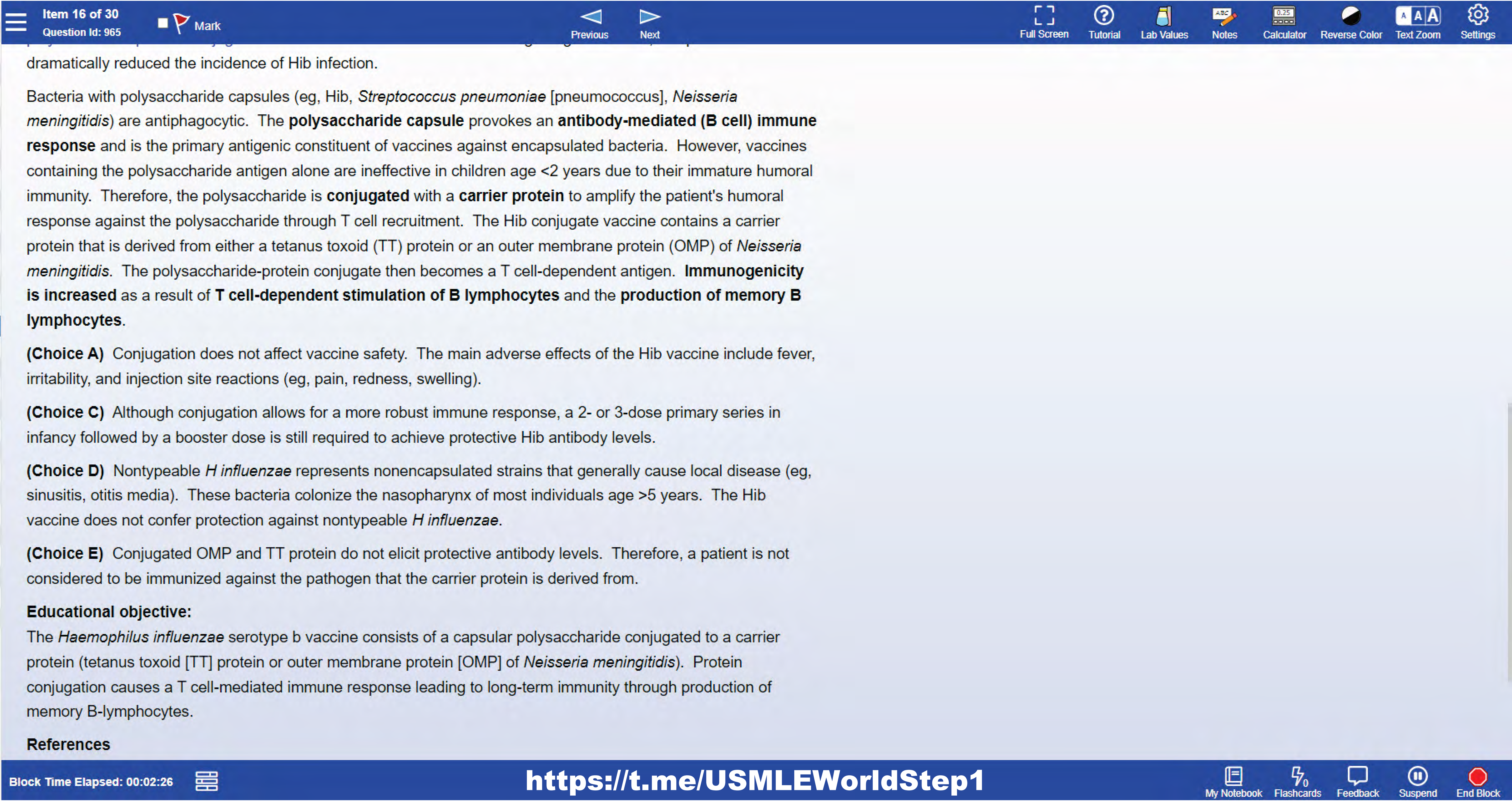


Explanation

Immunogenicity of polysaccharide vs conjugate vaccines		
Immunology	**Polysaccharide vaccine**	**Polysaccharide-protein conjugate vaccine**
Response type	B cell	B cell & T cell
Memory cell response	No	Yes
Relative duration of immunity	Short	Long
Immunogenicity in infancy	No	Yes

***Haemophilus influenzae* serotype b (Hib)**, an encapsulated gram-negative coccobacillus, was previously a common, invasive, and potentially fatal cause of pneumonia, epiglottitis, and meningitis in children. Neonates are protected with maternal anti-Hib IgG antibodies from placental transfer in utero, but this protection wanes as the immunoglobulins are degraded during the first few months of life. Therefore, widespread vaccination with the Hib polysaccharide-protein conjugate vaccine series is recommended starting at age 2 months; this practice has dramatically reduced the incidence of Hib infection.

Bacteria with polysaccharide capsules (eg, Hib, *Streptococcus pneumoniae* [pneumococcus], *Neisseria meningitidis*) are antiphagocytic. The **polysaccharide capsule** provokes an **antibody-mediated (B cell) immune response** and is the primary antigenic constituent of vaccines against encapsulated bacteria. However, vaccines containing the polysaccharide antigen alone are ineffective in children age <2 years due to their immature humoral immunity. Therefore, the polysaccharide is **conjugated** with a **carrier protein** to amplify the patient's humoral response against the polysaccharide through T cell recruitment. The Hib conjugate vaccine contains a carrier protein that is derived from either a tetanus toxoid (TT) protein or an outer membrane protein (OMP) of *Neisseria meningitidis*. The polysaccharide-protein conjugate then becomes a T cell-dependent antigen. **Immunogenicity is increased** as a result of **T cell-dependent stimulation of B lymphocytes** and the **production of memory B lymphocytes**.



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(Choice A) Conjugation does not affect vaccine safety. The main adverse effects of the Hib vaccine include fever, irritability, and injection site reactions (eg, pain, redness, swelling).

(Choice C) Although conjugation allows for a more robust immune response, a 2- or 3-dose primary series in infancy followed by a booster dose is still required to achieve protective Hib antibody levels.

(Choice D) Nontypeable *H influenzae* represents nonencapsulated strains that generally cause local disease (eg, sinusitis, otitis media). These bacteria colonize the nasopharynx of most individuals age >5 years. The Hib vaccine does not confer protection against nontypeable *H influenzae*.

(Choice E) Conjugated OMP and TT protein do not elicit protective antibody levels. Therefore, a patient is not considered to be immunized against the pathogen that the carrier protein is derived from.

Educational objective:

The *Haemophilus influenzae* serotype b vaccine consists of a capsular polysaccharide conjugated to a carrier protein (tetanus toxoid [TT] protein or outer membrane protein [OMP] of *Neisseria meningitidis*). Protein conjugation causes a T cell-mediated immune response leading to long-term immunity through production of memory B-lymphocytes.

References

Response type	B cell	B cell & T cell

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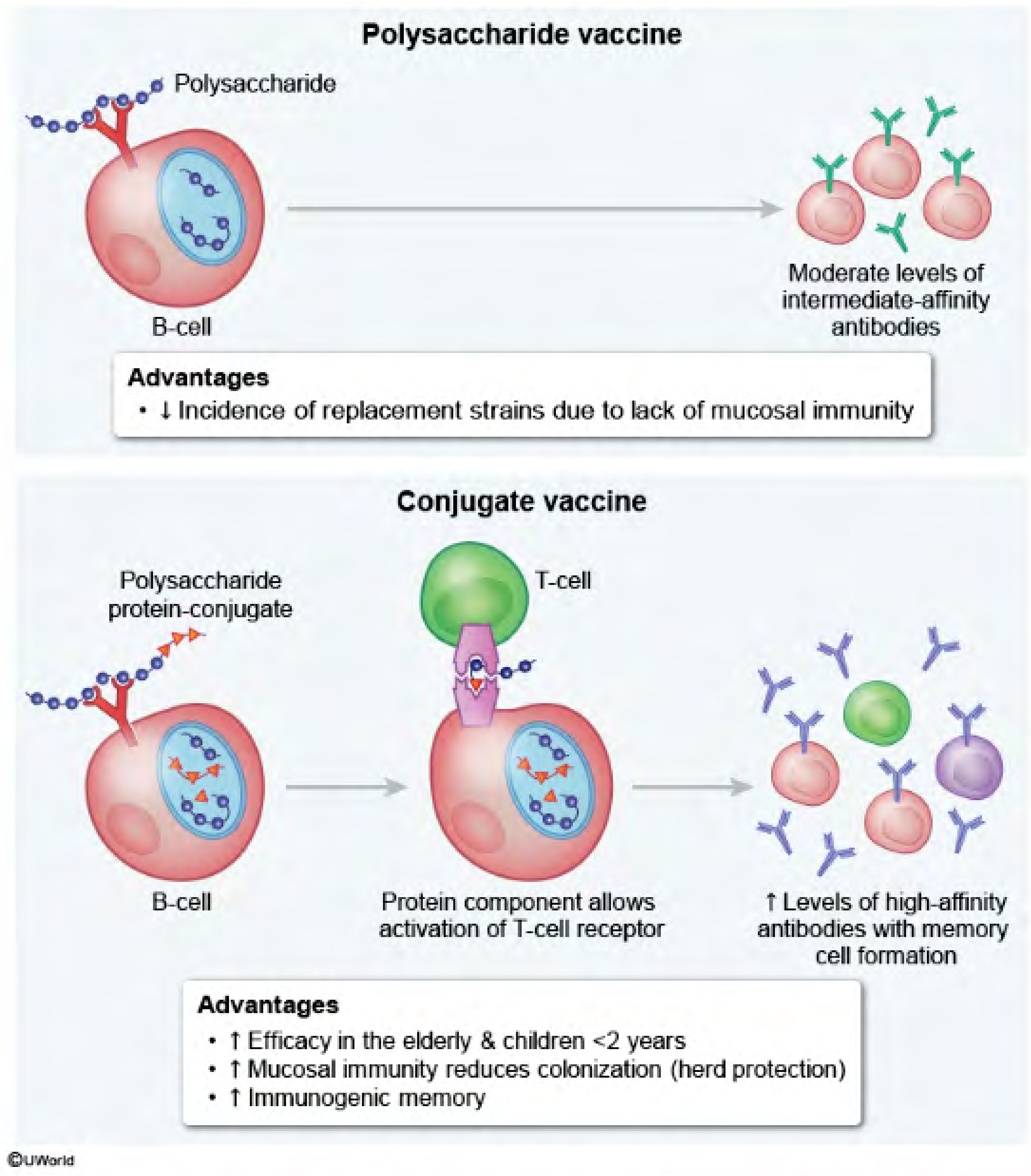
Polysaccharide vaccine
Polysaccharide
B-cell
Moderate levels of intermediate-affinity antibodies
Advantages
• ↓ Incidence of replacement strains due to lack of mucosal immunity
Conjugate vaccine
Polysaccharide protein-conjugate
T-cell
B-cell
Protein component allows activation of T-cell receptor
↑ Levels of high-affinity antibodies with memory cell formation
Advantages
• ↑ Efficacy in the elderly & children <2 years
• ↑ Mucosal immunity reduces colonization (herd protection)
• ↑ Immunogenic memory
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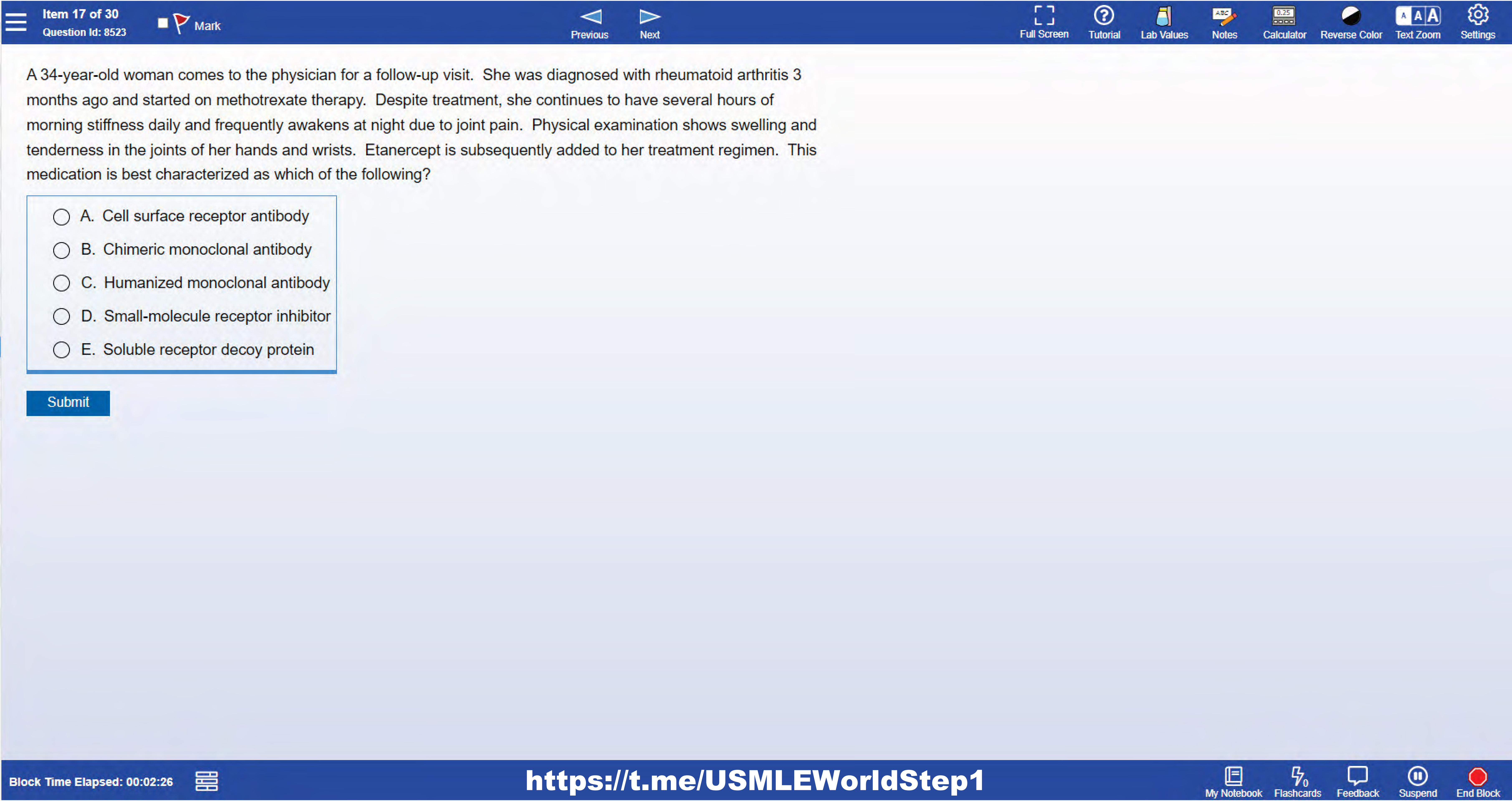
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A 34-year-old woman comes to the physician for a follow-up visit. She was diagnosed with rheumatoid arthritis 3 months ago and started on methotrexate therapy. Despite treatment, she continues to have several hours of morning stiffness daily and frequently awakens at night due to joint pain. Physical examination shows swelling and tenderness in the joints of her hands and wrists. Etanercept is subsequently added to her treatment regimen. This medication is best characterized as which of the following?

○ A. Cell surface receptor antibody
○ B. Chimeric monoclonal antibody
○ C. Humanized monoclonal antibody
○ D. Small-molecule receptor inhibitor
○ E. Soluble receptor decoy protein

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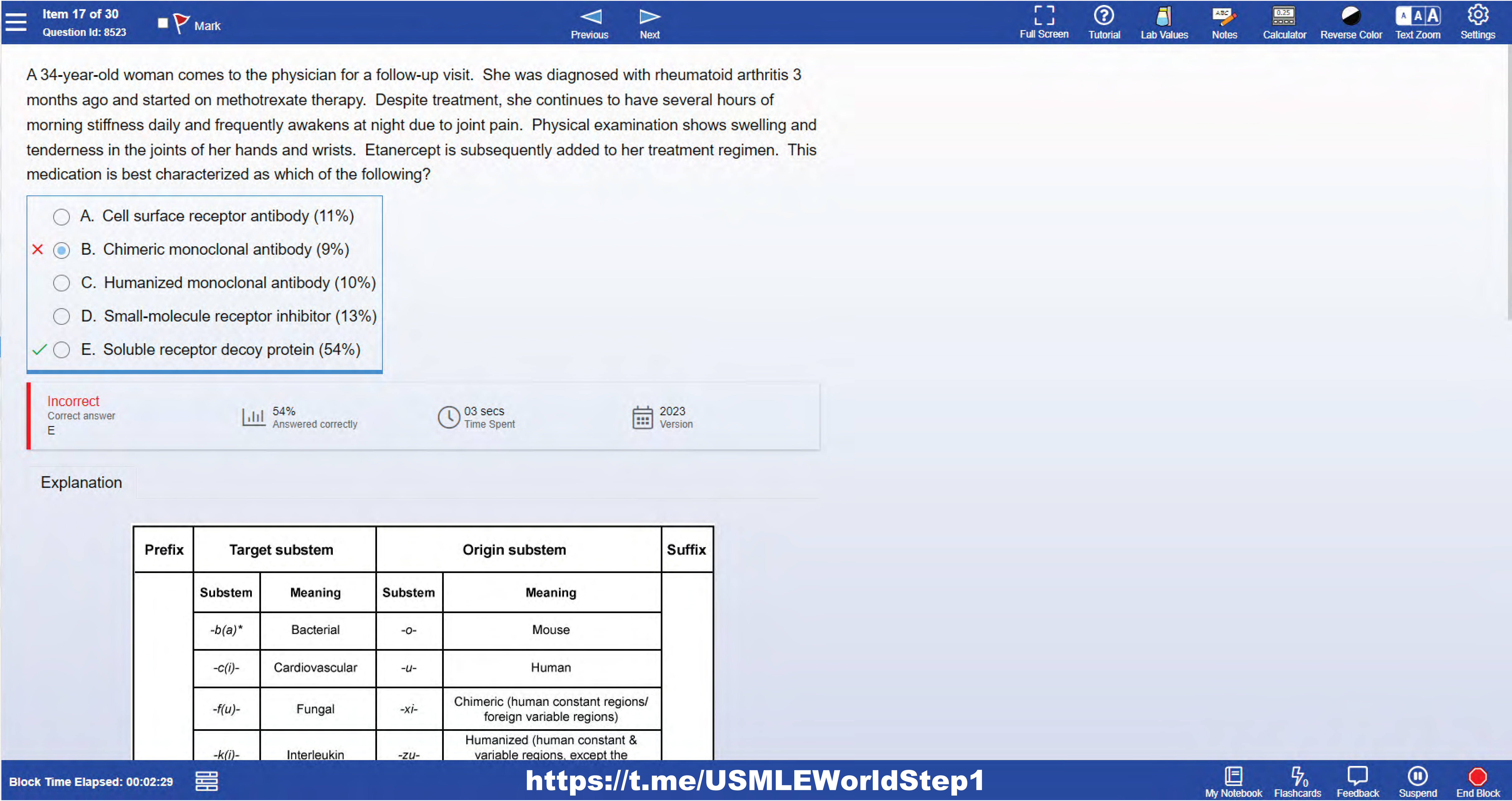
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A 34-year-old woman comes to the physician for a follow-up visit. She was diagnosed with rheumatoid arthritis 3 months ago and started on methotrexate therapy. Despite treatment, she continues to have several hours of morning stiffness daily and frequently awakens at night due to joint pain. Physical examination shows swelling and tenderness in the joints of her hands and wrists. Etanercept is subsequently added to her treatment regimen. This medication is best characterized as which of the following?

○ A. Cell surface receptor antibody (11%)
✗ ● B. Chimeric monoclonal antibody (9%)
○ C. Humanized monoclonal antibody (10%)
○ D. Small-molecule receptor inhibitor (13%)
✓ ○ E. Soluble receptor decoy protein (54%)

Incorrect
Correct answer
E

54%
Answered correctly

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Explanation

Prefix	Target substem		Origin substem		Suffix
	Substem	**Meaning**	**Substem**	**Meaning**	
	*-b(a)**	Bacterial	*-o-*	Mouse	
	-c(i)-	Cardiovascular	*-u-*	Human	
	-f(u)-	Fungal	*-xi-*	Chimeric (human constant regions/ foreign variable regions)	
	-k(i)-	Interleukin	*-zu-*	Humanized (human constant & variable regions, except the	

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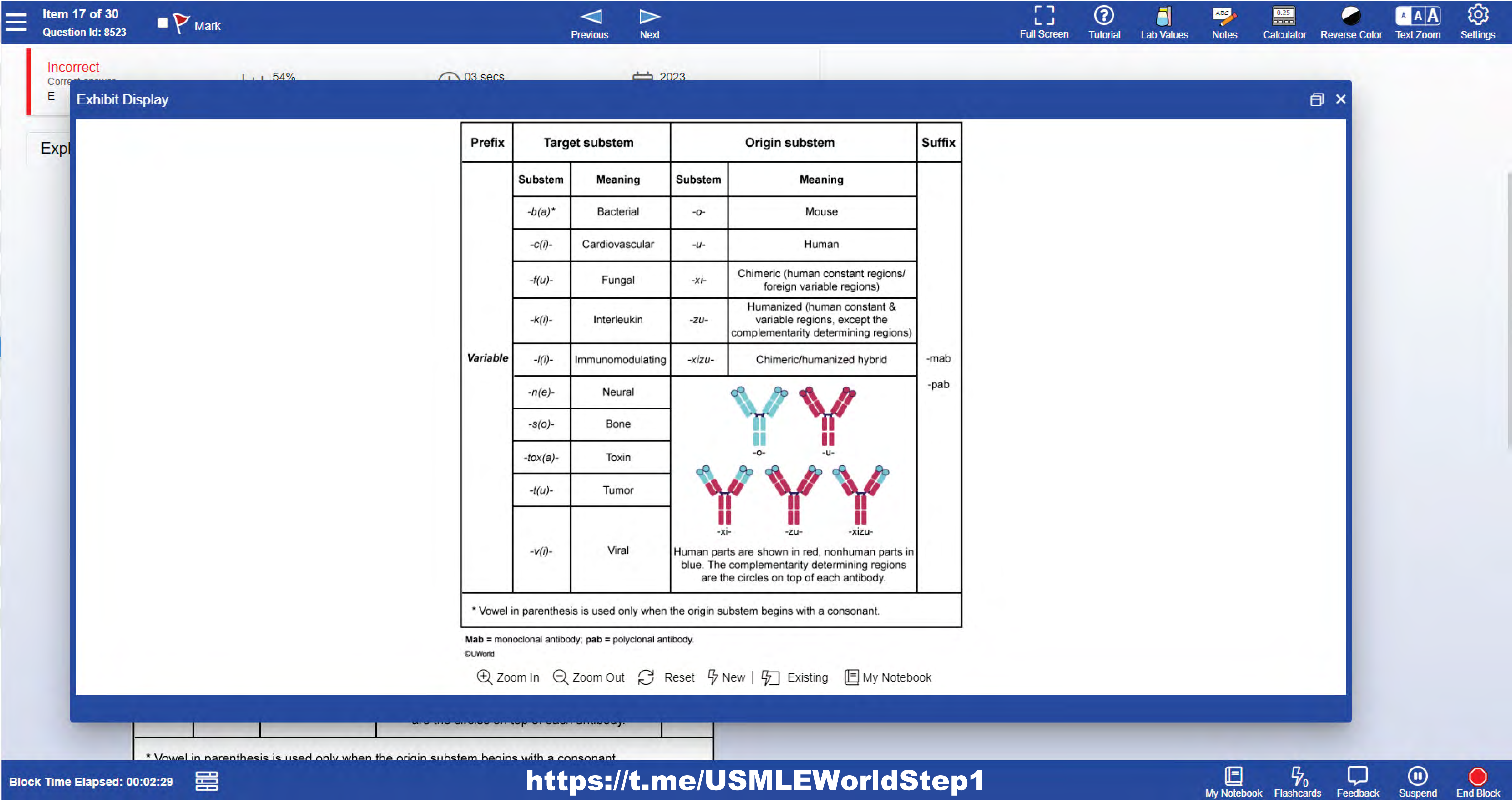
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Prefix	Target substem		Origin substem		Suffix
	Substem	Meaning	Substem	Meaning	
Variable	-*b(a)**	Bacterial	-*o*-	Mouse	-mab -pab
	-*c(i)*-	Cardiovascular	-*u*-	Human	
	-*f(u)*-	Fungal	-*xi*-	Chimeric (human constant regions/ foreign variable regions)	
	-*k(i)*-	Interleukin	-*zu*-	Humanized (human constant & variable regions, except the complementarity determining regions)	
	-*l(i)*-	Immunomodulating	-*xizu*-	Chimeric/humanized hybrid	
	-*n(e)*-	Neural	Human parts are shown in red, nonhuman parts in blue. The complementarity determining regions are the circles on top of each antibody.		
	-*s(o)*-	Bone			
	-*tox(a)*-	Toxin			
	-*t(u)*-	Tumor			
	-*v(i)*-	Viral			

* Vowel in parenthesis is used only when the origin substem begins with a consonant.

Mab = monoclonal antibody; **pab** = polyclonal antibody.

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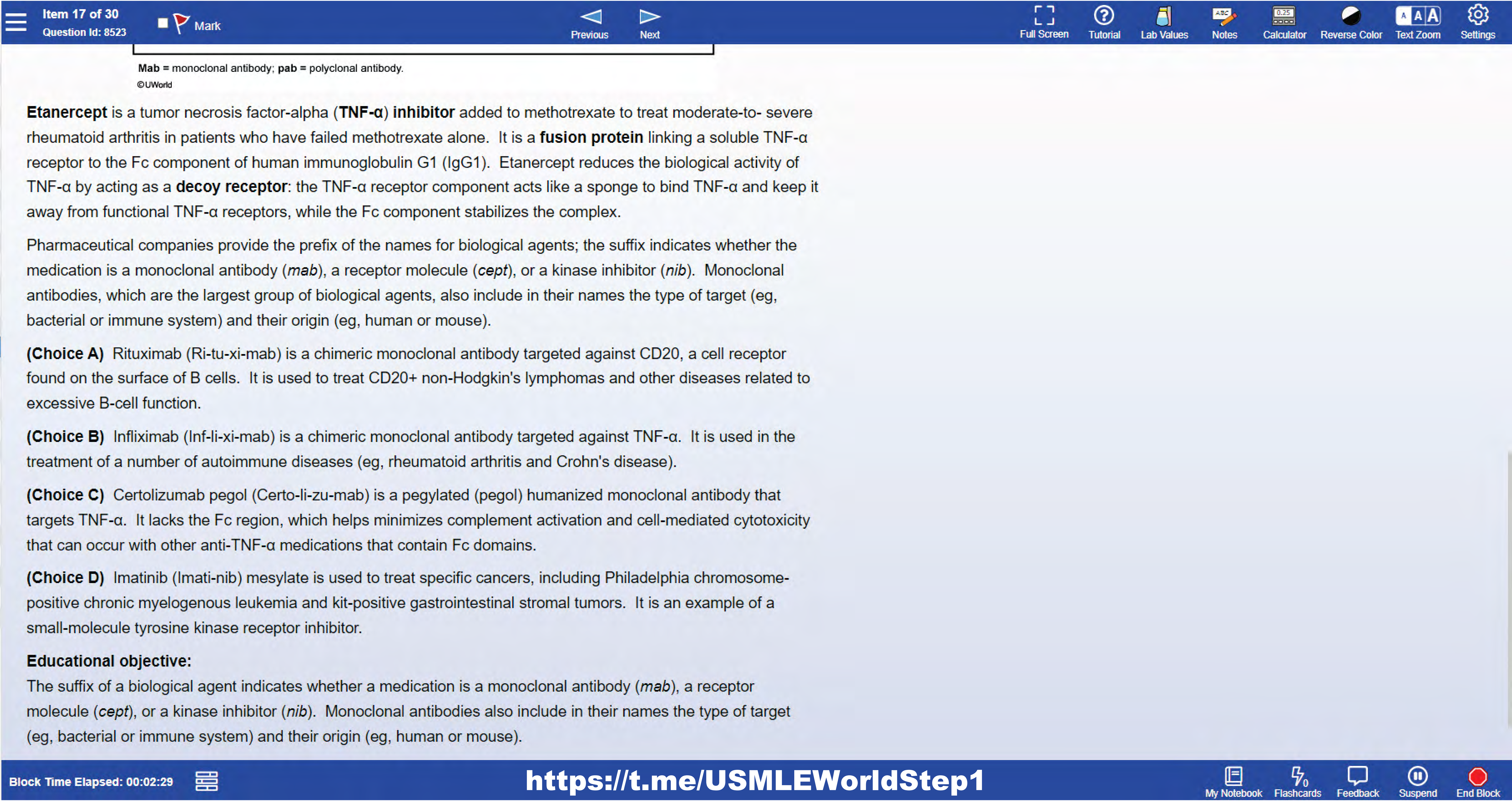

Mab = monoclonal antibody; **pab** = polyclonal antibody.

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Etanercept is a tumor necrosis factor-alpha (**TNF-α**) **inhibitor** added to methotrexate to treat moderate-to- severe rheumatoid arthritis in patients who have failed methotrexate alone. It is a **fusion protein** linking a soluble TNF-α receptor to the Fc component of human immunoglobulin G1 (IgG1). Etanercept reduces the biological activity of TNF-α by acting as a **decoy receptor**: the TNF-α receptor component acts like a sponge to bind TNF-α and keep it away from functional TNF-α receptors, while the Fc component stabilizes the complex.

Pharmaceutical companies provide the prefix of the names for biological agents; the suffix indicates whether the medication is a monoclonal antibody (*mab*), a receptor molecule (*cept*), or a kinase inhibitor (*nib*). Monoclonal antibodies, which are the largest group of biological agents, also include in their names the type of target (eg, bacterial or immune system) and their origin (eg, human or mouse).

(Choice A) Rituximab (Ri-tu-xi-mab) is a chimeric monoclonal antibody targeted against CD20, a cell receptor found on the surface of B cells. It is used to treat CD20+ non-Hodgkin's lymphomas and other diseases related to excessive B-cell function.

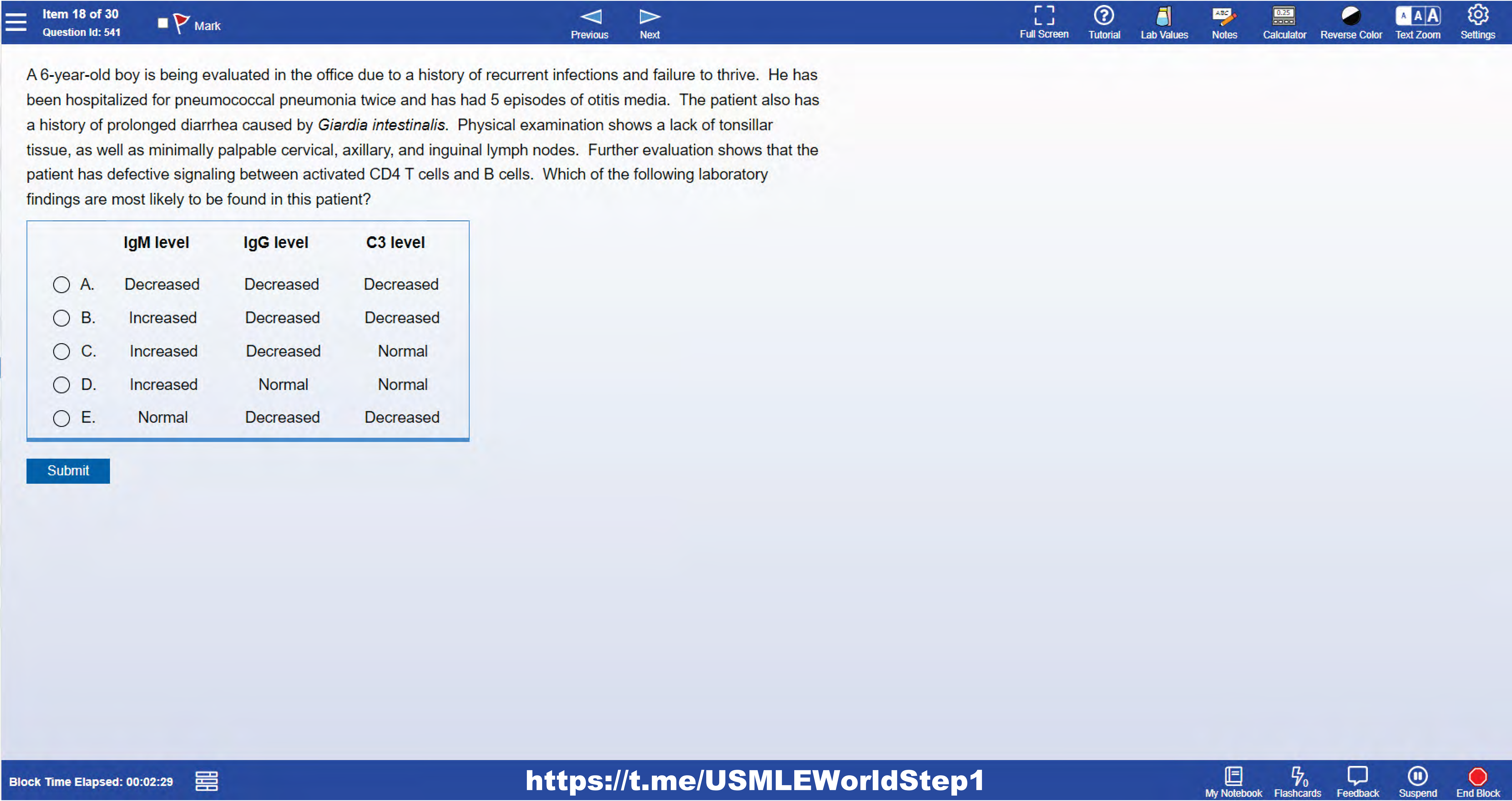
(Choice B) Infliximab (Inf-li-xi-mab) is a chimeric monoclonal antibody targeted against TNF-α. It is used in the treatment of a number of autoimmune diseases (eg, rheumatoid arthritis and Crohn's disease).

(Choice C) Certolizumab pegol (Certo-li-zu-mab) is a pegylated (pegol) humanized monoclonal antibody that targets TNF-α. It lacks the Fc region, which helps minimizes complement activation and cell-mediated cytotoxicity that can occur with other anti-TNF-α medications that contain Fc domains.

(Choice D) Imatinib (Imati-nib) mesylate is used to treat specific cancers, including Philadelphia chromosome-positive chronic myelogenous leukemia and kit-positive gastrointestinal stromal tumors. It is an example of a small-molecule tyrosine kinase receptor inhibitor.

Educational objective:

The suffix of a biological agent indicates whether a medication is a monoclonal antibody (*mab*), a receptor molecule (*cept*), or a kinase inhibitor (*nib*). Monoclonal antibodies also include in their names the type of target (eg, bacterial or immune system) and their origin (eg, human or mouse).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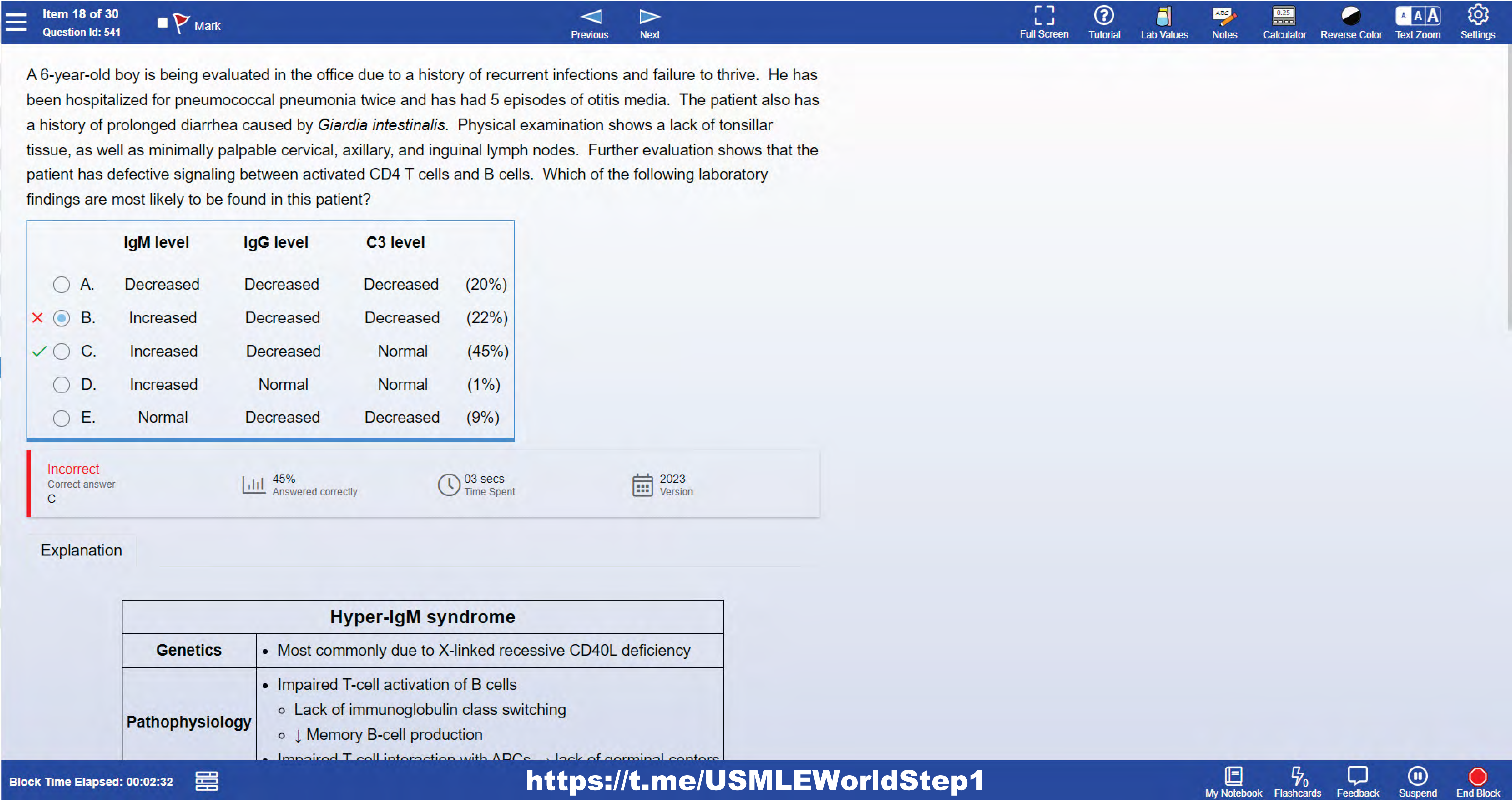
A 6-year-old boy is being evaluated in the office due to a history of recurrent infections and failure to thrive. He has been hospitalized for pneumococcal pneumonia twice and has had 5 episodes of otitis media. The patient also has a history of prolonged diarrhea caused by *Giardia intestinalis*. Physical examination shows a lack of tonsillar tissue, as well as minimally palpable cervical, axillary, and inguinal lymph nodes. Further evaluation shows that the patient has defective signaling between activated CD4 T cells and B cells. Which of the following laboratory findings are most likely to be found in this patient?

	IgM level	**IgG level**	**C3 level**
○ A.	Decreased	Decreased	Decreased
○ B.	Increased	Decreased	Decreased
○ C.	Increased	Decreased	Normal
○ D.	Increased	Normal	Normal
○ E.	Normal	Decreased	Decreased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		IgM level	**IgG level**	**C3 level**	
	○ A.	Decreased	Decreased	Decreased	(20%)
✗	● B.	Increased	Decreased	Decreased	(22%)
✓	○ C.	Increased	Decreased	Normal	(45%)
	○ D.	Increased	Normal	Normal	(1%)
	○ E.	Normal	Decreased	Decreased	(9%)

Incorrect
Correct answer
C

45%
Answered correctly

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Explanation

Hyper-IgM syndrome	
Genetics	• Most commonly due to X-linked recessive CD40L deficiency
Pathophysiology	• Impaired T-cell activation of B cells ∘ Lack of immunoglobulin class switching ∘ ↓ Memory B-cell production • Impaired T-cell interaction with APCs → lack of germinal centers

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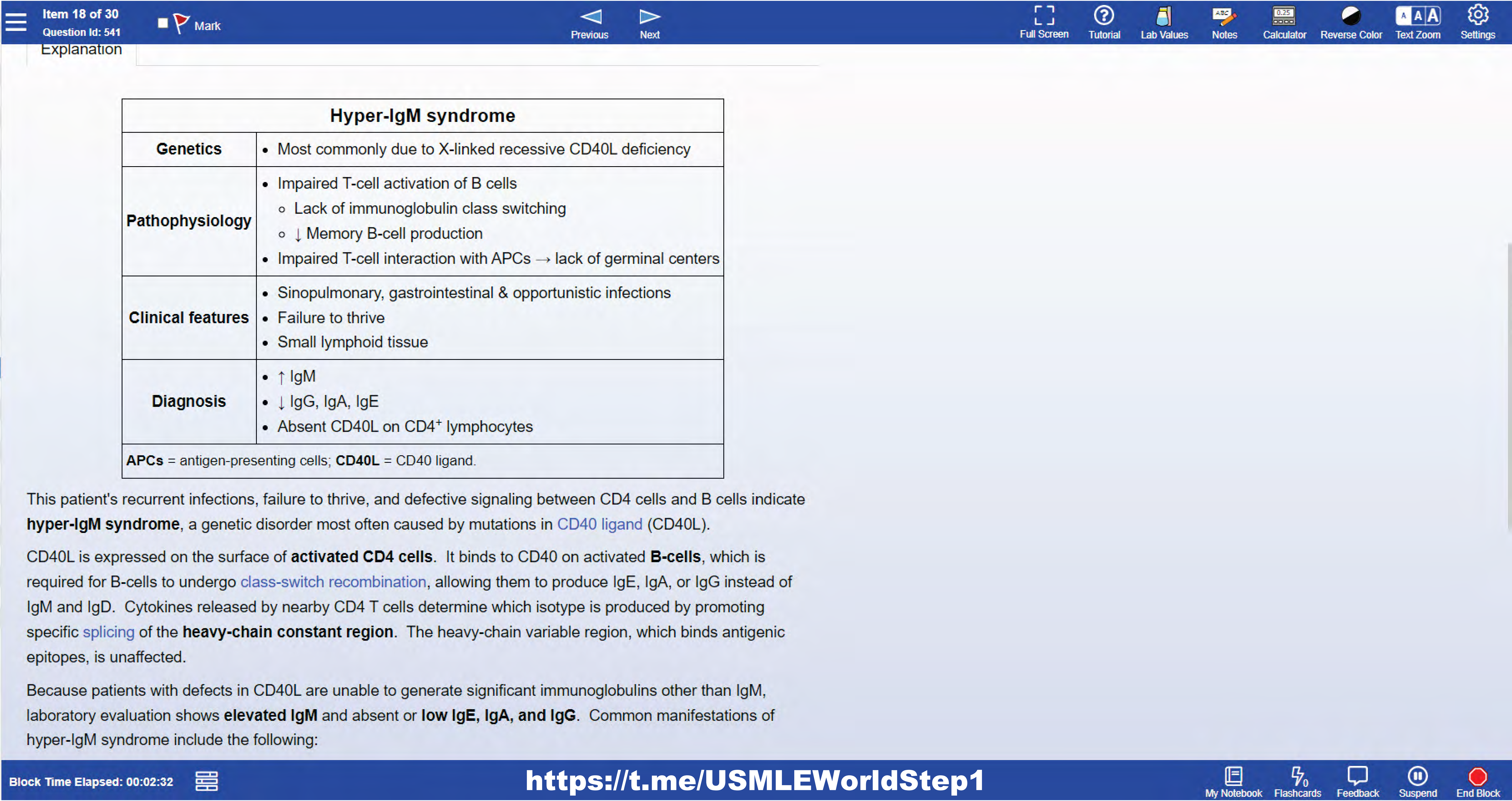
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Hyper-IgM syndrome	
Genetics	• Most commonly due to X-linked recessive CD40L deficiency
Pathophysiology	• Impaired T-cell activation of B cells ∘ Lack of immunoglobulin class switching ∘ ↓ Memory B-cell production • Impaired T-cell interaction with APCs → lack of germinal centers
Clinical features	• Sinopulmonary, gastrointestinal & opportunistic infections • Failure to thrive • Small lymphoid tissue
Diagnosis	• ↑ IgM • ↓ IgG, IgA, IgE • Absent CD40L on $CD4^+$ lymphocytes

APCs = antigen-presenting cells; **CD40L** = CD40 ligand.

This patient's recurrent infections, failure to thrive, and defective signaling between CD4 cells and B cells indicate **hyper-IgM syndrome**, a genetic disorder most often caused by mutations in CD40 ligand (CD40L).

CD40L is expressed on the surface of **activated CD4 cells**. It binds to CD40 on activated **B-cells**, which is required for B-cells to undergo class-switch recombination, allowing them to produce IgE, IgA, or IgG instead of IgM and IgD. Cytokines released by nearby CD4 T cells determine which isotype is produced by promoting specific splicing of the **heavy-chain constant region**. The heavy-chain variable region, which binds antigenic epitopes, is unaffected.

Because patients with defects in CD40L are unable to generate significant immunoglobulins other than IgM, laboratory evaluation shows **elevated IgM** and absent or **low IgE, IgA, and IgG**. Common manifestations of hyper-IgM syndrome include the following:

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Because patients with defects in CD40L are unable to generate significant immunoglobulins other than IgM, laboratory evaluation shows **elevated IgM** and absent or **low IgE, IgA, and IgG**. Common manifestations of hyper-IgM syndrome include the following:

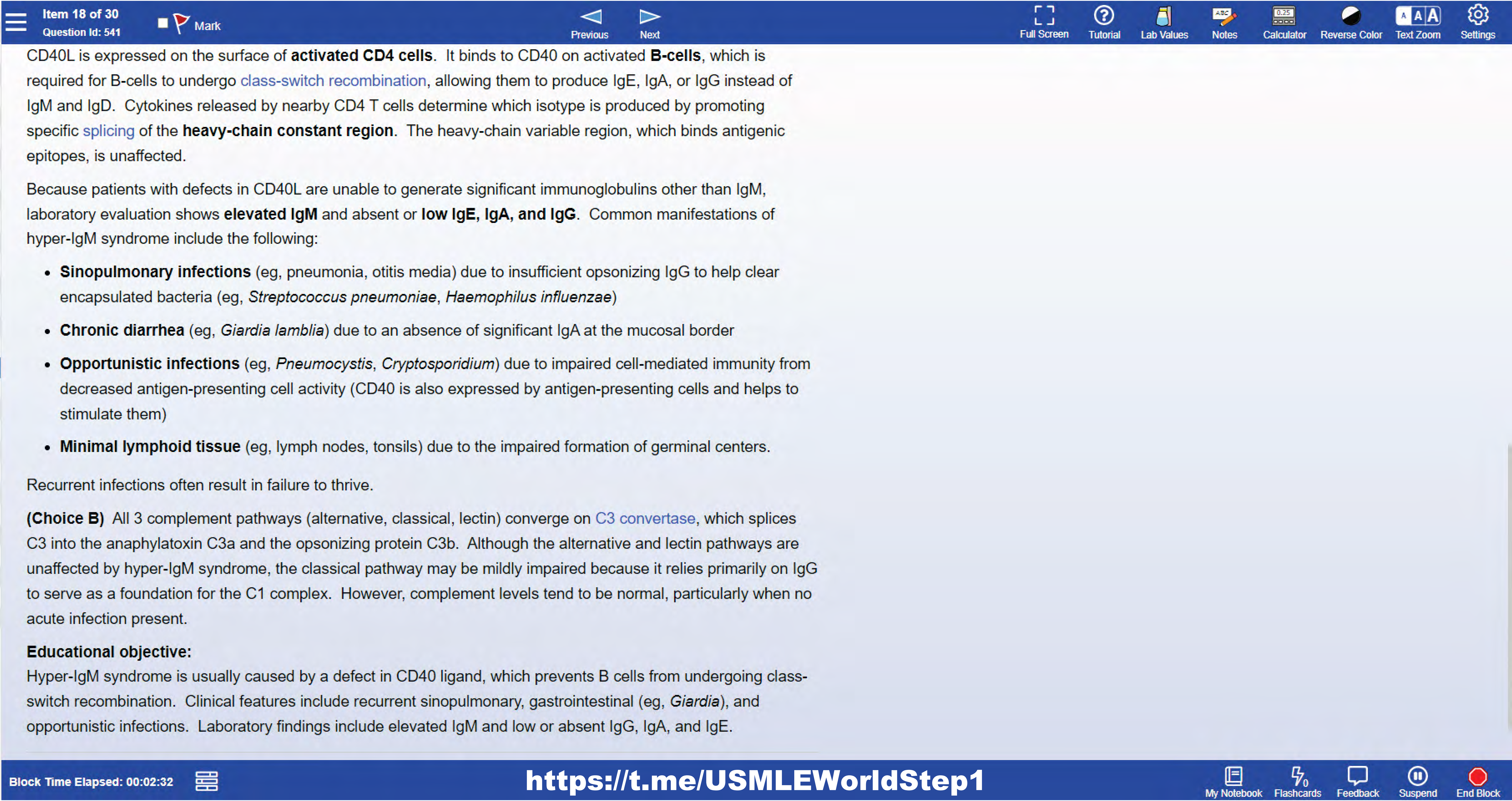
- **Sinopulmonary infections** (eg, pneumonia, otitis media) due to insufficient opsonizing IgG to help clear encapsulated bacteria (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*)
- **Chronic diarrhea** (eg, *Giardia lamblia*) due to an absence of significant IgA at the mucosal border
- **Opportunistic infections** (eg, *Pneumocystis*, *Cryptosporidium*) due to impaired cell-mediated immunity from decreased antigen-presenting cell activity (CD40 is also expressed by antigen-presenting cells and helps to stimulate them)
- **Minimal lymphoid tissue** (eg, lymph nodes, tonsils) due to the impaired formation of germinal centers.

Recurrent infections often result in failure to thrive.

(Choice B) All 3 complement pathways (alternative, classical, lectin) converge on C3 convertase, which splices C3 into the anaphylatoxin C3a and the opsonizing protein C3b. Although the alternative and lectin pathways are unaffected by hyper-IgM syndrome, the classical pathway may be mildly impaired because it relies primarily on IgG to serve as a foundation for the C1 complex. However, complement levels tend to be normal, particularly when no acute infection present.

Educational objective:

Hyper-IgM syndrome is usually caused by a defect in CD40 ligand, which prevents B cells from undergoing class



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Because patients with defects in CD40L are unable to generate significant immunoglobulins other than IgM, laboratory evaluation shows **elevated IgM** and absent or **low IgE, IgA, and IgG**. Common manifestations of hyper-IgM syndrome include the following:

- **Sinopulmonary infections** (eg, pneumonia, otitis media) due to insufficient opsonizing IgG to help clear encapsulated bacteria (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*)
- **Chronic diarrhea** (eg, *Giardia lamblia*) due to an absence of significant IgA at the mucosal border
- **Opportunistic infections** (eg, *Pneumocystis*, *Cryptosporidium*) due to impaired cell-mediated immunity from decreased antigen-presenting cell activity (CD40 is also expressed by antigen-presenting cells and helps to stimulate them)
- **Minimal lymphoid tissue** (eg, lymph nodes, tonsils) due to the impaired formation of germinal centers.

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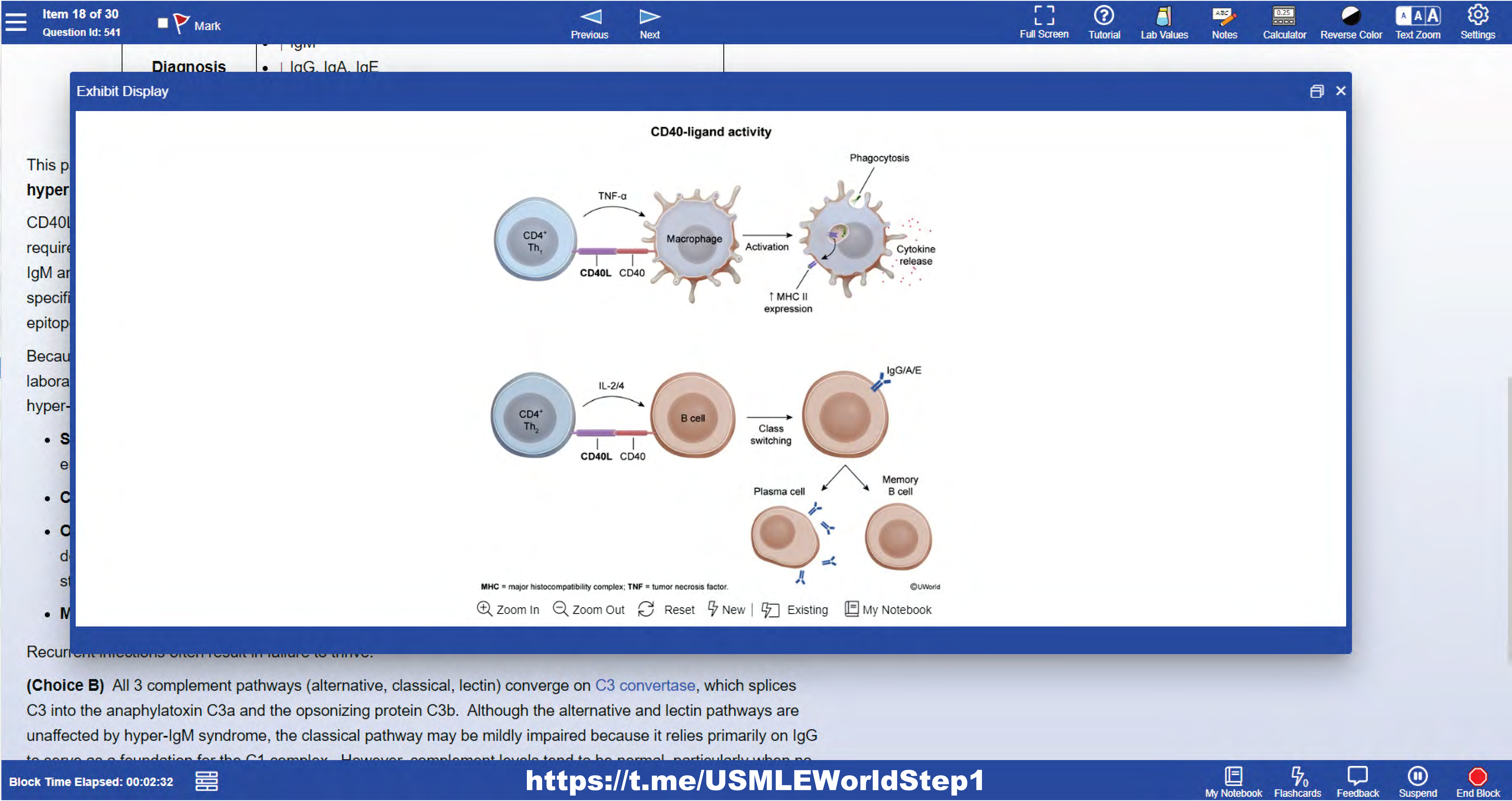
Educational objective:
Hyper-IgM syndrome is usually caused by a defect in CD40 ligand, which prevents B cells from undergoing class-switch recombination. Clinical features include recurrent sinopulmonary, gastrointestinal (eg, *Giardia*), and opportunistic infections. Laboratory findings include elevated IgM and low or absent IgG, IgA, and IgE.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TNF-α
CD4⁺ Th₁
Macrophage
CD40L
CD40
Activation
Phagocytosis
Cytokine release
↑ MHC II expression
IL-2/4
CD4⁺ Th₂
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Diagnosis

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CD40-ligand activity

MHC = major histocompatibility complex; **TNF** = tumor necrosis factor.

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Recurrent infections often result in failure to thrive.

(Choice B) All 3 complement pathways (alternative, classical, lectin) converge on C3 convertase, which splices C3 into the anaphylatoxin C3a and the opsonizing protein C3b. Although the alternative and lectin pathways are unaffected by hyper-IgM syndrome, the classical pathway may be mildly impaired because it relies primarily on IgG to serve as a foundation for the C1 complex. However, complement levels tend to be normal, particularly when no

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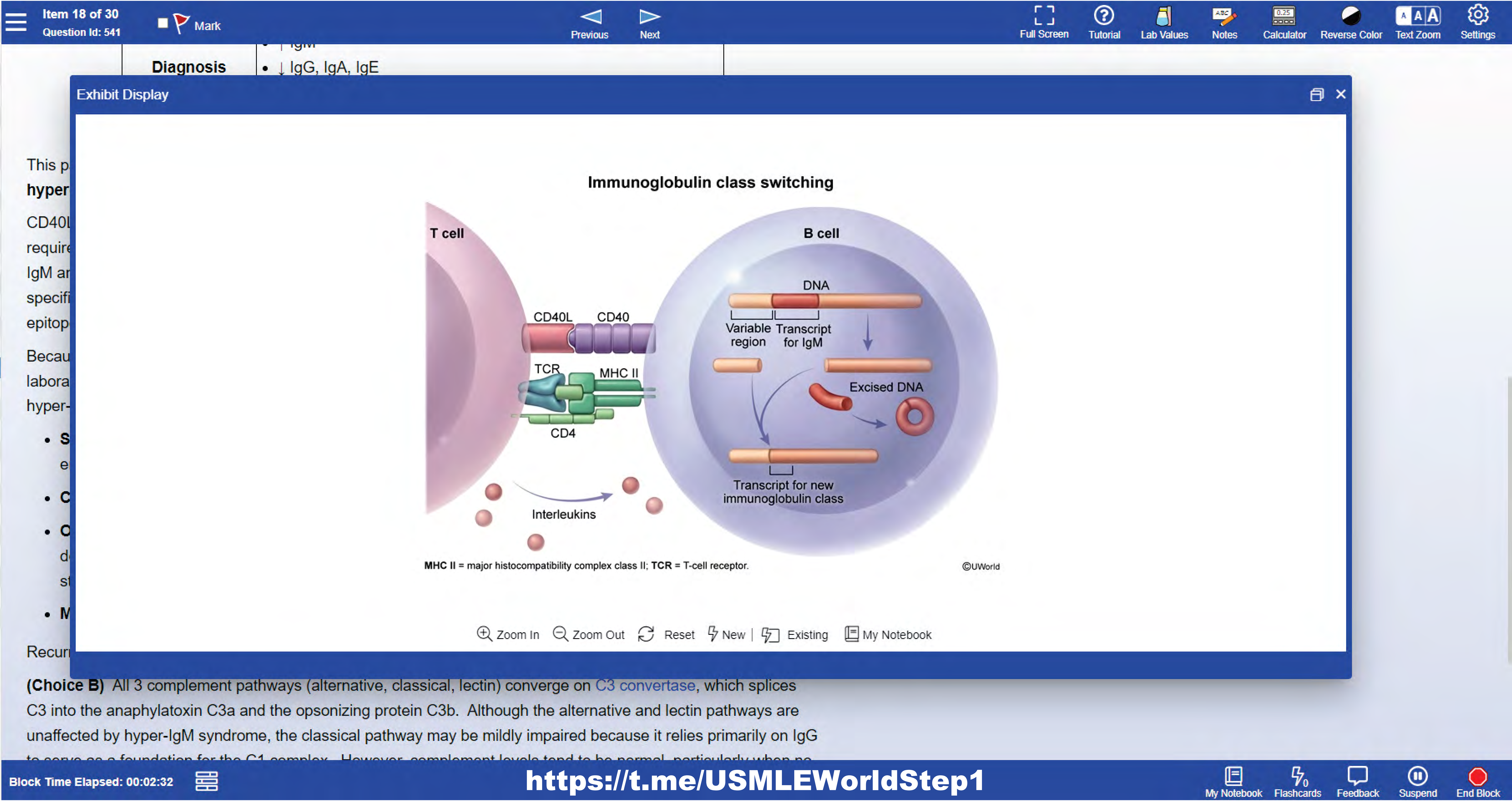
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Diagnosis	• ↓ IgG, IgA, IgE

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Immunoglobulin class switching

MHC II = major histocompatibility complex class II; **TCR** = T-cell receptor.

(Choice B) All 3 complement pathways (alternative, classical, lectin) converge on C3 convertase, which splices C3 into the anaphylatoxin C3a and the opsonizing protein C3b. Although the alternative and lectin pathways are unaffected by hyper-IgM syndrome, the classical pathway may be mildly impaired because it relies primarily on IgG to serve as a foundation for the C1 complex. However, complement levels tend to be normal, particularly when no

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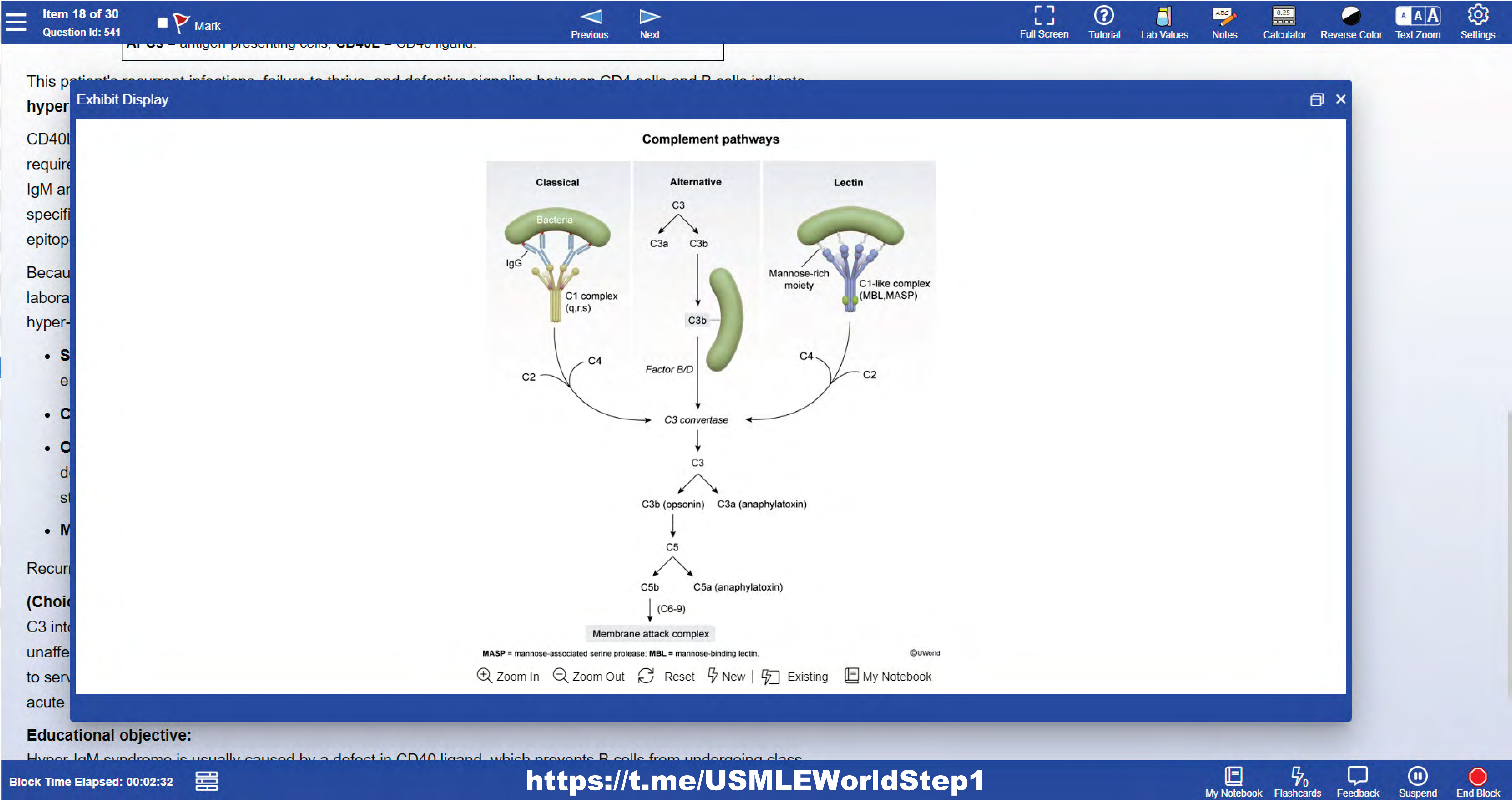
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C3
C3a
C3b
C3b
Factor B/D
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C1-like complex
(MBL,MASP)
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C4
C4
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C3 convertase
C3
C3b (opsonin)
C3a (anaphylatoxin)
C5
C5b
C5a (anaphylatoxin)
(C6-9)
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APCs = antigen presenting cells; CD40L = CD40 ligand.

This patient's recurrent infections, failure to thrive, and defective signaling between CD4 cells and B cells indicate

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Complement pathways

MASP = mannose-associated serine protease; **MBL** = mannose-binding lectin.

Educational objective:

Hyper IgM syndrome is usually caused by a defect in CD40 ligand, which prevents B cells from undergoing class

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A 68-year-old man comes to the emergency department with a 2-day history of fever, chills, and productive cough. His temperature is 38.9 C (102 F), blood pressure is 108/52 mm Hg, pulse is 102/min, and respirations are 26/min. Crackles and bronchial breath sounds are heard over the right lower lung. There is dullness to percussion over the same area. Chest x-ray reveals right lower lobe consolidation and a right-sided pleural effusion. The patient is started on the appropriate treatment, and a diagnostic thoracentesis is performed that shows an uncomplicated parapneumonic effusion. When a sterile sample of the inflammatory exudate is experimentally introduced into normal human tissue, rapid neutrophil locomotion is observed. Which of the following components of the exudate is most likely responsible for this observed effect?

○ A. Bradykinin
○ B. C4a
○ C. IFN-γ
○ D. IL-4
○ E. Leukotriene B_4
○ F. Thromboxane A_2

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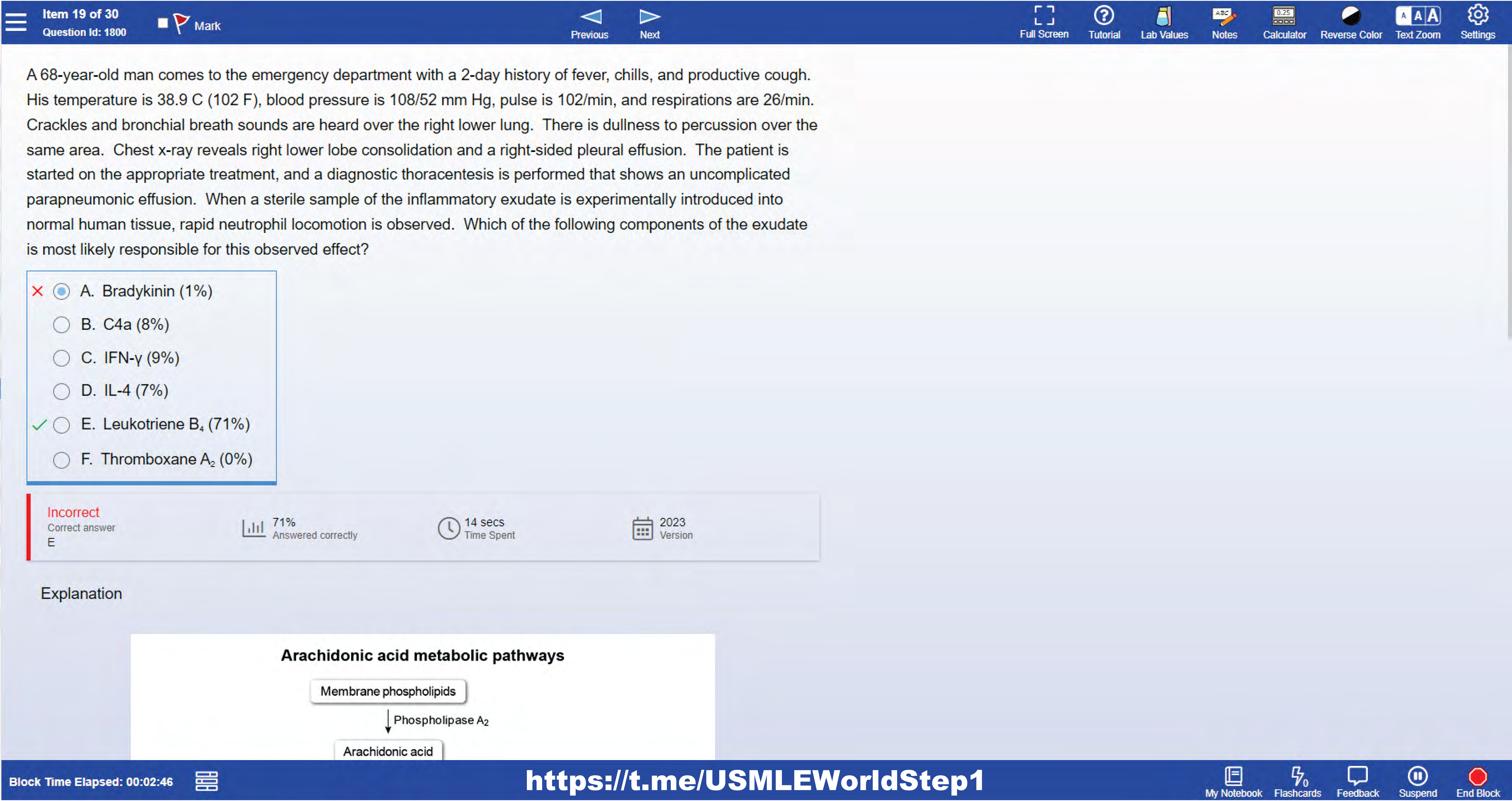
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- ✗ ● A. Bradykinin (1%)
- ○ B. C4a (8%)
- ○ C. IFN-γ (9%)
- ○ D. IL-4 (7%)
- ✓ ○ E. Leukotriene B_4 (71%)
- ○ F. Thromboxane A_2 (0%)

Incorrect
Correct answer
E

71%
Answered correctly

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Time Spent

2023
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Explanation

Arachidonic acid metabolic pathways

Membrane phospholipids
Phospholipase A₂
Arachidonic acid

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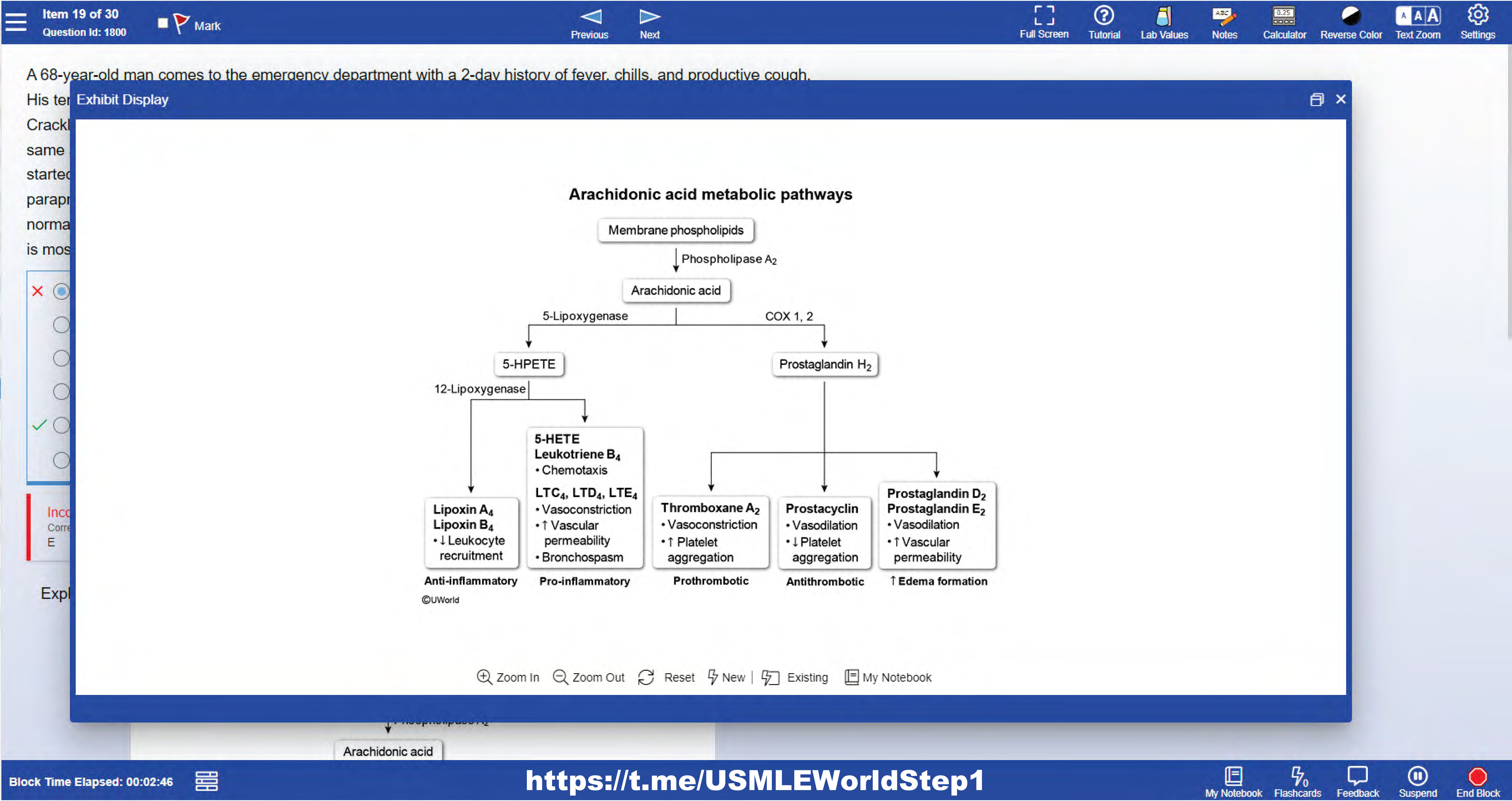
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Arachidonic acid metabolic pathways

Membrane phospholipids
Phospholipase A2
Arachidonic acid
5-Lipoxygenase
COX 1, 2
5-HPETE
Prostaglandin H2
12-Lipoxygenase
5-HETE
Leukotriene B4
• Chemotaxis
LTC4, LTD4, LTE4
• Vasoconstriction
• ↑ Vascular permeability
• Bronchospasm
Lipoxin A4
Lipoxin B4
• ↓ Leukocyte recruitment
Thromboxane A2
• Vasoconstriction
• ↑ Platelet aggregation
Prostacyclin
• Vasodilation
• ↓ Platelet aggregation
Prostaglandin D2
Prostaglandin E2
• Vasodilation
• ↑ Vascular permeability
Anti-inflammatory
Pro-inflammatory
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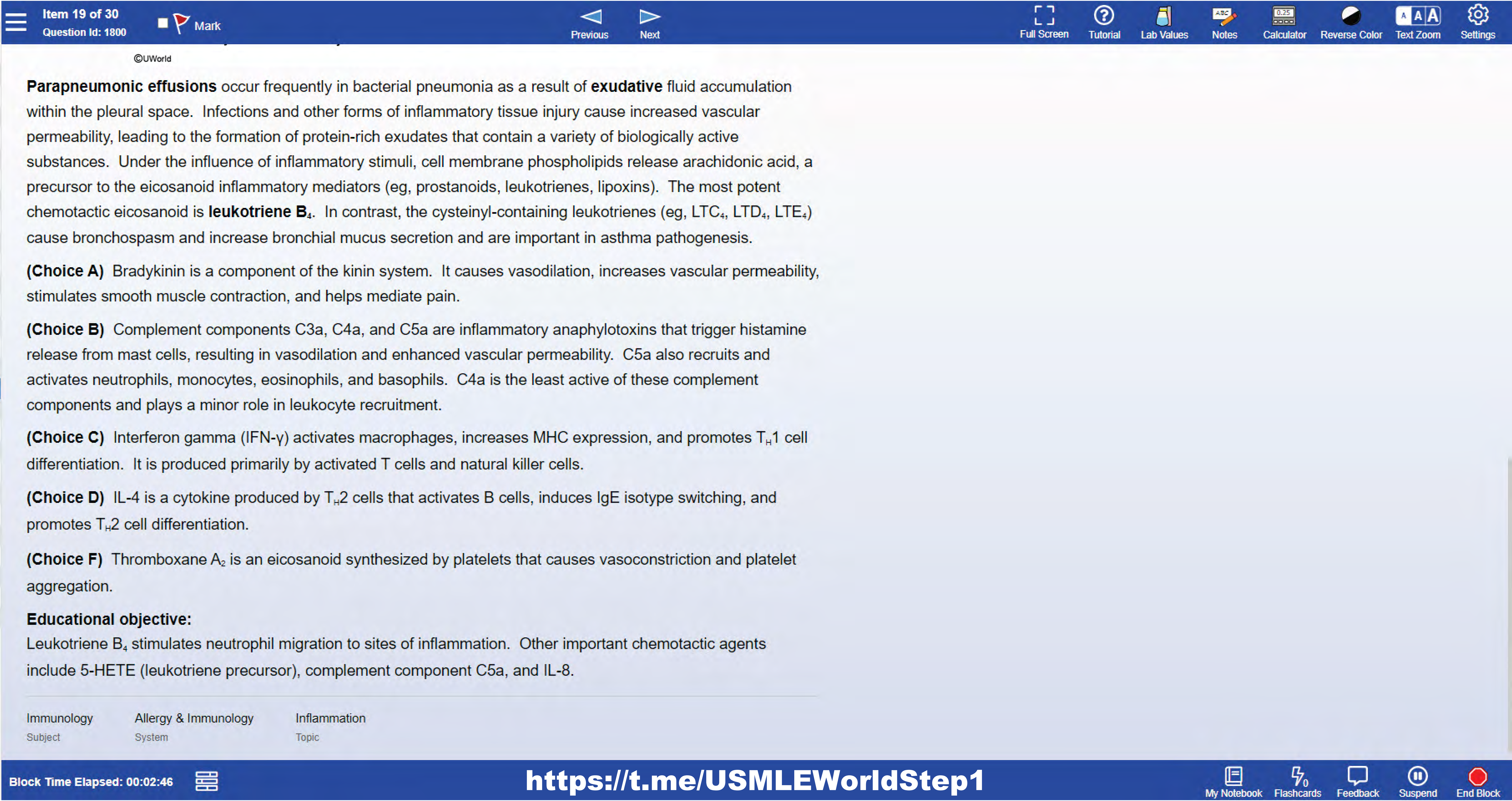
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Parapneumonic effusions occur frequently in bacterial pneumonia as a result of **exudative** fluid accumulation within the pleural space. Infections and other forms of inflammatory tissue injury cause increased vascular permeability, leading to the formation of protein-rich exudates that contain a variety of biologically active substances. Under the influence of inflammatory stimuli, cell membrane phospholipids release arachidonic acid, a precursor to the eicosanoid inflammatory mediators (eg, prostanoids, leukotrienes, lipoxins). The most potent chemotactic eicosanoid is **leukotriene B_4**. In contrast, the cysteinyl-containing leukotrienes (eg, LTC_4, LTD_4, LTE_4) cause bronchospasm and increase bronchial mucus secretion and are important in asthma pathogenesis.

(Choice A) Bradykinin is a component of the kinin system. It causes vasodilation, increases vascular permeability, stimulates smooth muscle contraction, and helps mediate pain.

(Choice B) Complement components C3a, C4a, and C5a are inflammatory anaphylotoxins that trigger histamine release from mast cells, resulting in vasodilation and enhanced vascular permeability. C5a also recruits and activates neutrophils, monocytes, eosinophils, and basophils. C4a is the least active of these complement components and plays a minor role in leukocyte recruitment.

(Choice C) Interferon gamma (IFN-γ) activates macrophages, increases MHC expression, and promotes T_H1 cell differentiation. It is produced primarily by activated T cells and natural killer cells.

(Choice D) IL-4 is a cytokine produced by T_H2 cells that activates B cells, induces IgE isotype switching, and promotes T_H2 cell differentiation.

(Choice F) Thromboxane A_2 is an eicosanoid synthesized by platelets that causes vasoconstriction and platelet aggregation.

Educational objective:
Leukotriene B_4 stimulates neutrophil migration to sites of inflammation. Other important chemotactic agents include 5-HETE (leukotriene precursor), complement component C5a, and IL-8.

Immunology	Allergy & Immunology	Inflammation
Subject	System	Topic

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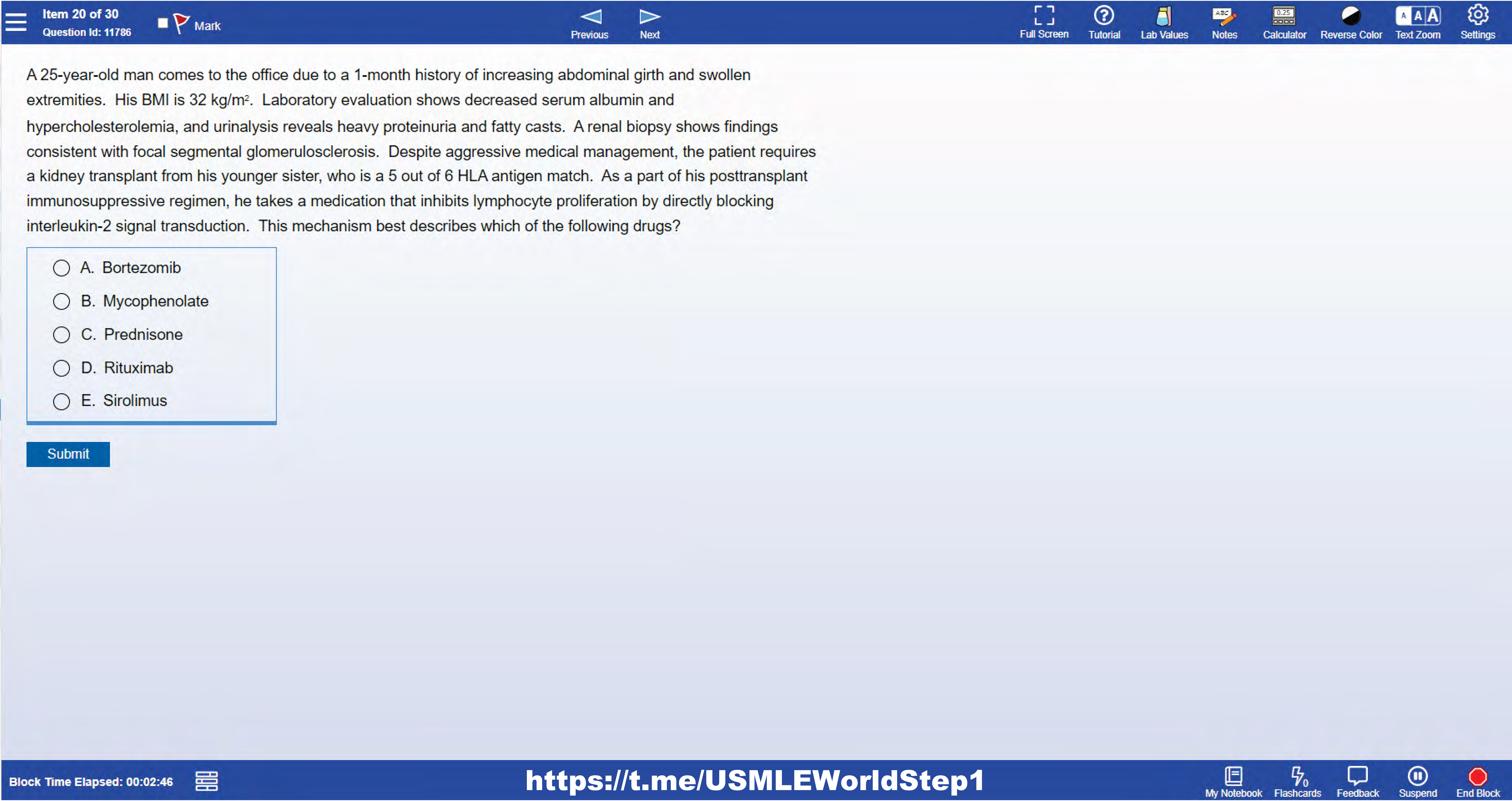
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A 25-year-old man comes to the office due to a 1-month history of increasing abdominal girth and swollen extremities. His BMI is 32 kg/m^2. Laboratory evaluation shows decreased serum albumin and hypercholesterolemia, and urinalysis reveals heavy proteinuria and fatty casts. A renal biopsy shows findings consistent with focal segmental glomerulosclerosis. Despite aggressive medical management, the patient requires a kidney transplant from his younger sister, who is a 5 out of 6 HLA antigen match. As a part of his posttransplant immunosuppressive regimen, he takes a medication that inhibits lymphocyte proliferation by directly blocking interleukin-2 signal transduction. This mechanism best describes which of the following drugs?

○ A. Bortezomib
○ B. Mycophenolate
○ C. Prednisone
○ D. Rituximab
○ E. Sirolimus

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○ A. Bortezomib (7%)
✗ ● B. Mycophenolate (8%)
○ C. Prednisone (7%)
○ D. Rituximab (15%)
✓ ○ E. Sirolimus (61%)

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Correct answer
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61%
Answered correctly

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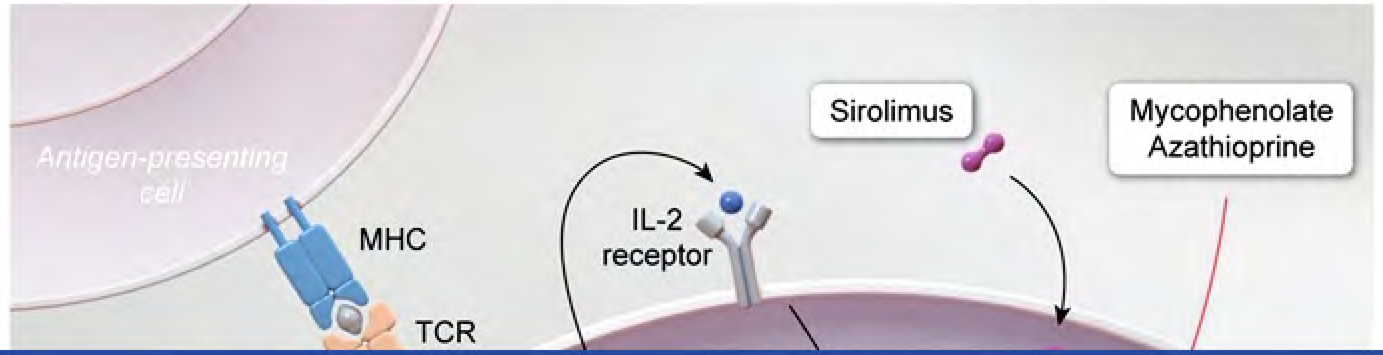
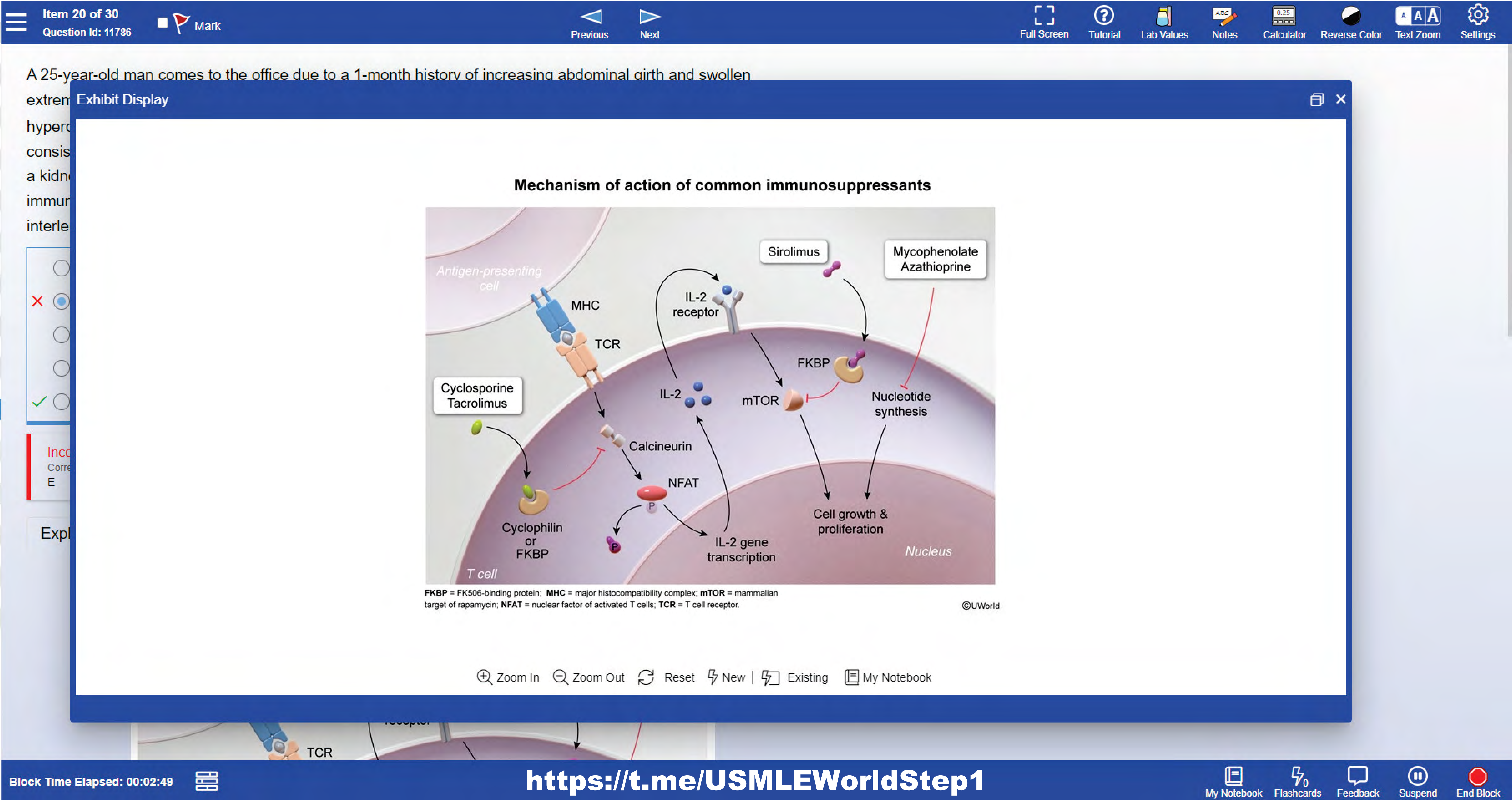
Explanation

Mechanism of action of common immunosuppressants

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Antigen-presenting cell
MHC
TCR
IL-2 receptor
Sirolimus
Mycophenolate
Azathioprine
FKBP
Cyclosporine
Tacrolimus
IL-2
mTOR
Nucleotide synthesis
Calcineurin
NFAT
P
Cyclophilin or FKBP
IL-2 gene transcription
Cell growth & proliferation
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Mechanism of action of common immunosuppressants

FKBP = FK506-binding protein; **MHC** = major histocompatibility complex; **mTOR** = mammalian target of rapamycin; **NFAT** = nuclear factor of activated T cells; **TCR** = T cell receptor.

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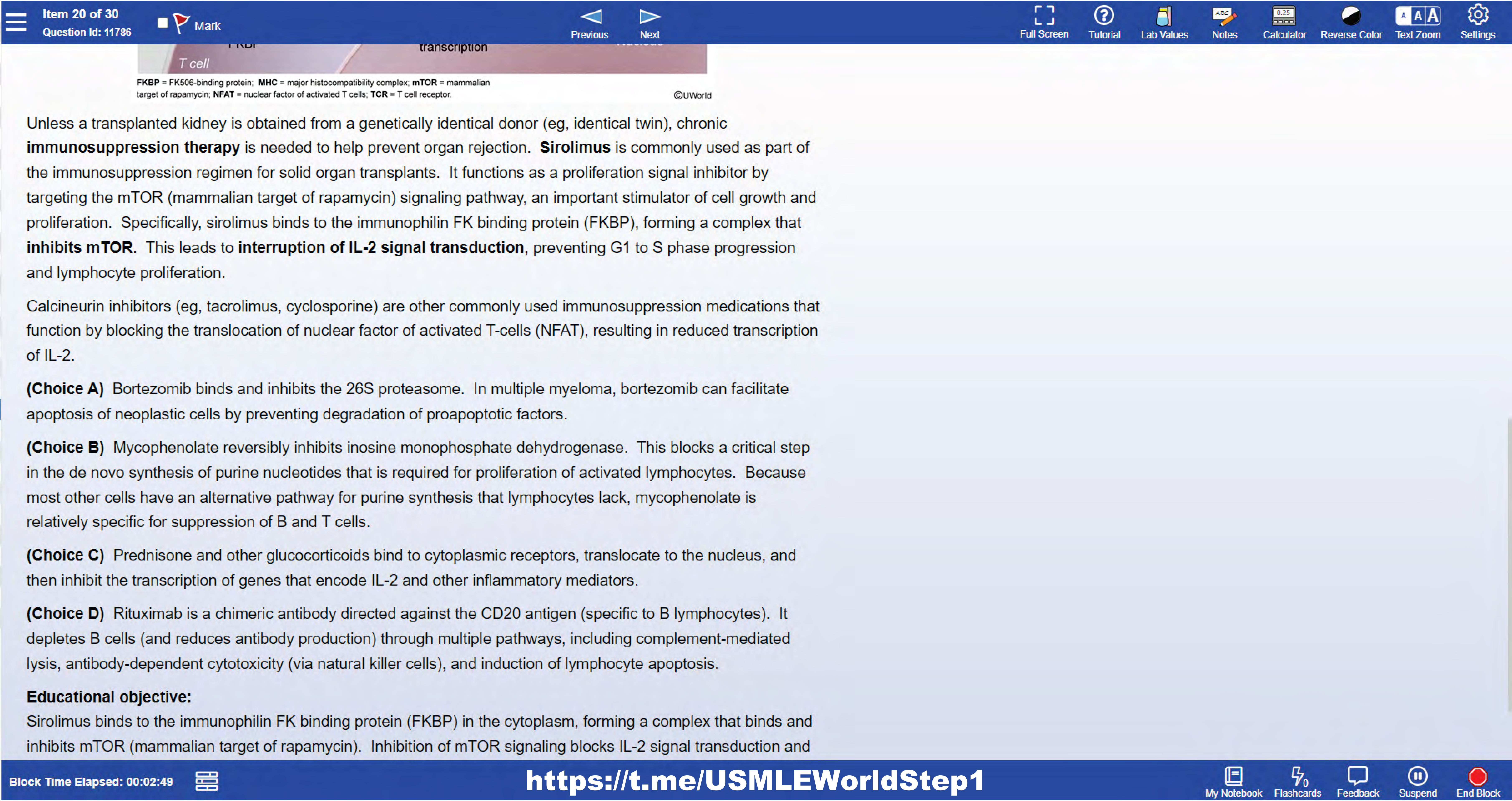

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Unless a transplanted kidney is obtained from a genetically identical donor (eg, identical twin), chronic **immunosuppression therapy** is needed to help prevent organ rejection. **Sirolimus** is commonly used as part of the immunosuppression regimen for solid organ transplants. It functions as a proliferation signal inhibitor by targeting the mTOR (mammalian target of rapamycin) signaling pathway, an important stimulator of cell growth and proliferation. Specifically, sirolimus binds to the immunophilin FK binding protein (FKBP), forming a complex that **inhibits mTOR**. This leads to **interruption of IL-2 signal transduction**, preventing G1 to S phase progression and lymphocyte proliferation.

Calcineurin inhibitors (eg, tacrolimus, cyclosporine) are other commonly used immunosuppression medications that function by blocking the translocation of nuclear factor of activated T-cells (NFAT), resulting in reduced transcription of IL-2.

(Choice A) Bortezomib binds and inhibits the 26S proteasome. In multiple myeloma, bortezomib can facilitate apoptosis of neoplastic cells by preventing degradation of proapoptotic factors.

(Choice B) Mycophenolate reversibly inhibits inosine monophosphate dehydrogenase. This blocks a critical step in the de novo synthesis of purine nucleotides that is required for proliferation of activated lymphocytes. Because most other cells have an alternative pathway for purine synthesis that lymphocytes lack, mycophenolate is relatively specific for suppression of B and T cells.

(Choice C) Prednisone and other glucocorticoids bind to cytoplasmic receptors, translocate to the nucleus, and then inhibit the transcription of genes that encode IL-2 and other inflammatory mediators.

(Choice D) Rituximab is a chimeric antibody directed against the CD20 antigen (specific to B lymphocytes). It depletes B cells (and reduces antibody production) through multiple pathways, including complement-mediated lysis, antibody-dependent cytotoxicity (via natural killer cells), and induction of lymphocyte apoptosis.

Educational objective:

Sirolimus binds to the immunophilin FK binding protein (FKBP) in the cytoplasm, forming a complex that binds and inhibits mTOR (mammalian target of rapamycin). Inhibition of mTOR signaling blocks IL-2 signal transduction and

immunosuppression therapy is needed to help prevent organ rejection. **Sirolimus** is commonly used as part of the immunosuppression regimen for solid organ transplants. It functions as a proliferation signal inhibitor by targeting the mTOR (mammalian target of rapamycin) signaling pathway, an important stimulator of cell growth and proliferation. Specifically, sirolimus binds to the immunophilin FK binding protein (FKBP), forming a complex that **inhibits mTOR**. This leads to **interruption of IL-2 signal transduction**, preventing G1 to S phase progression and lymphocyte proliferation.

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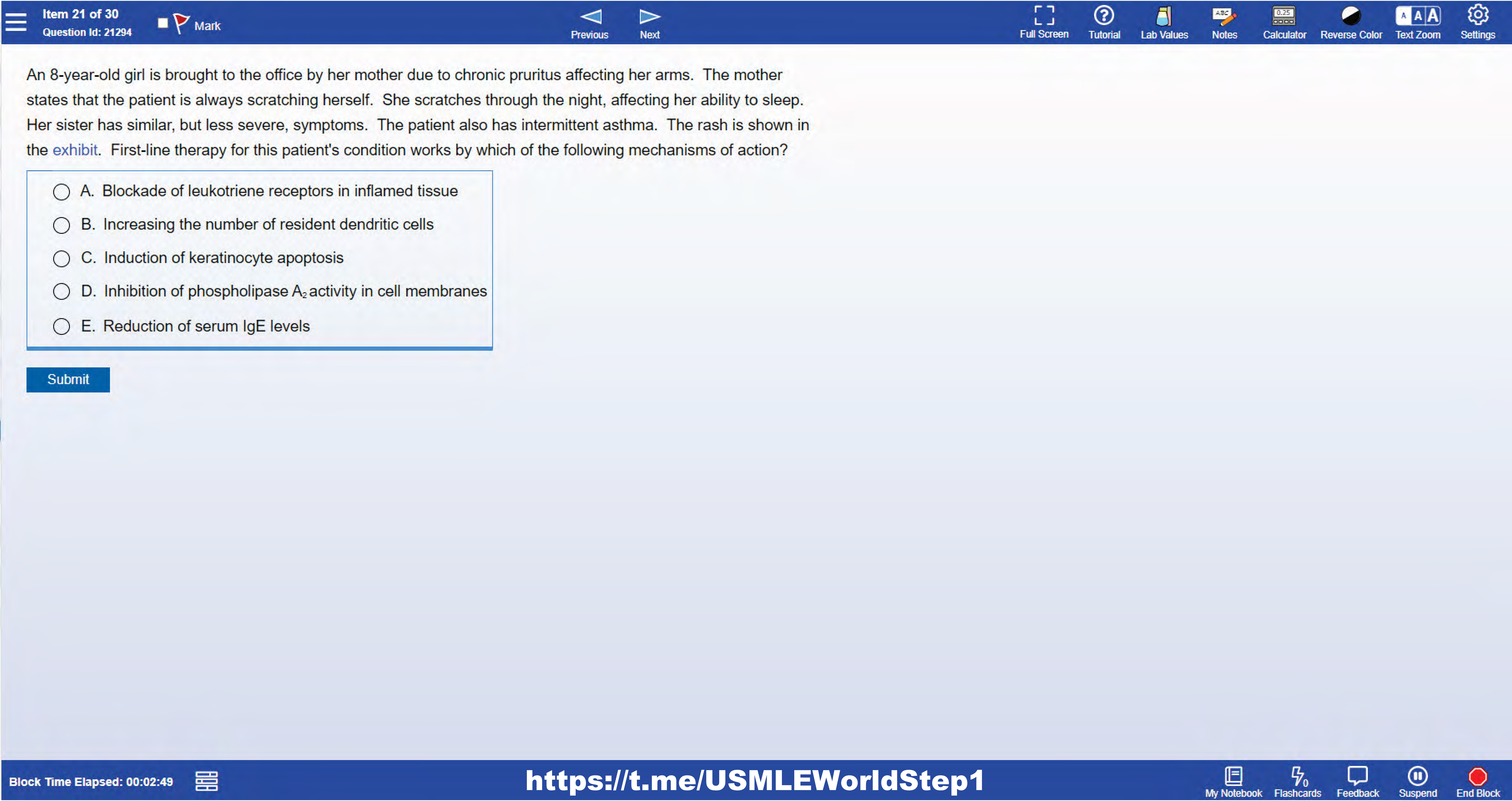
Immunology	Allergy & Immunology	Transplant rejection
Subject	System	Topic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An 8-year-old girl is brought to the office by her mother due to chronic pruritus affecting her arms. The mother states that the patient is always scratching herself. She scratches through the night, affecting her ability to sleep. Her sister has similar, but less severe, symptoms. The patient also has intermittent asthma. The rash is shown in the exhibit. First-line therapy for this patient's condition works by which of the following mechanisms of action?

○ A. Blockade of leukotriene receptors in inflamed tissue
○ B. Increasing the number of resident dendritic cells
○ C. Induction of keratinocyte apoptosis
○ D. Inhibition of phospholipase A_2 activity in cell membranes
○ E. Reduction of serum IgE levels

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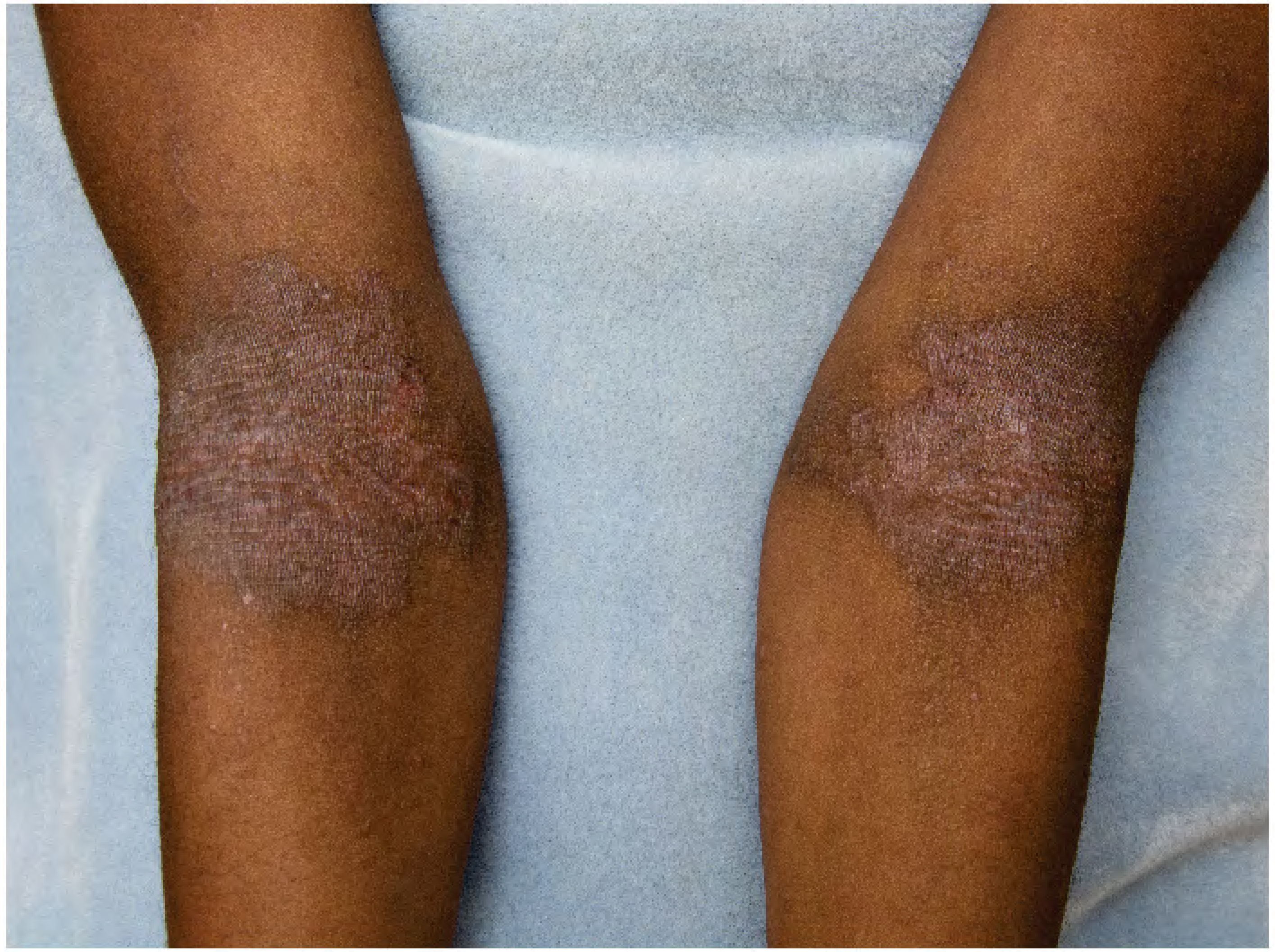

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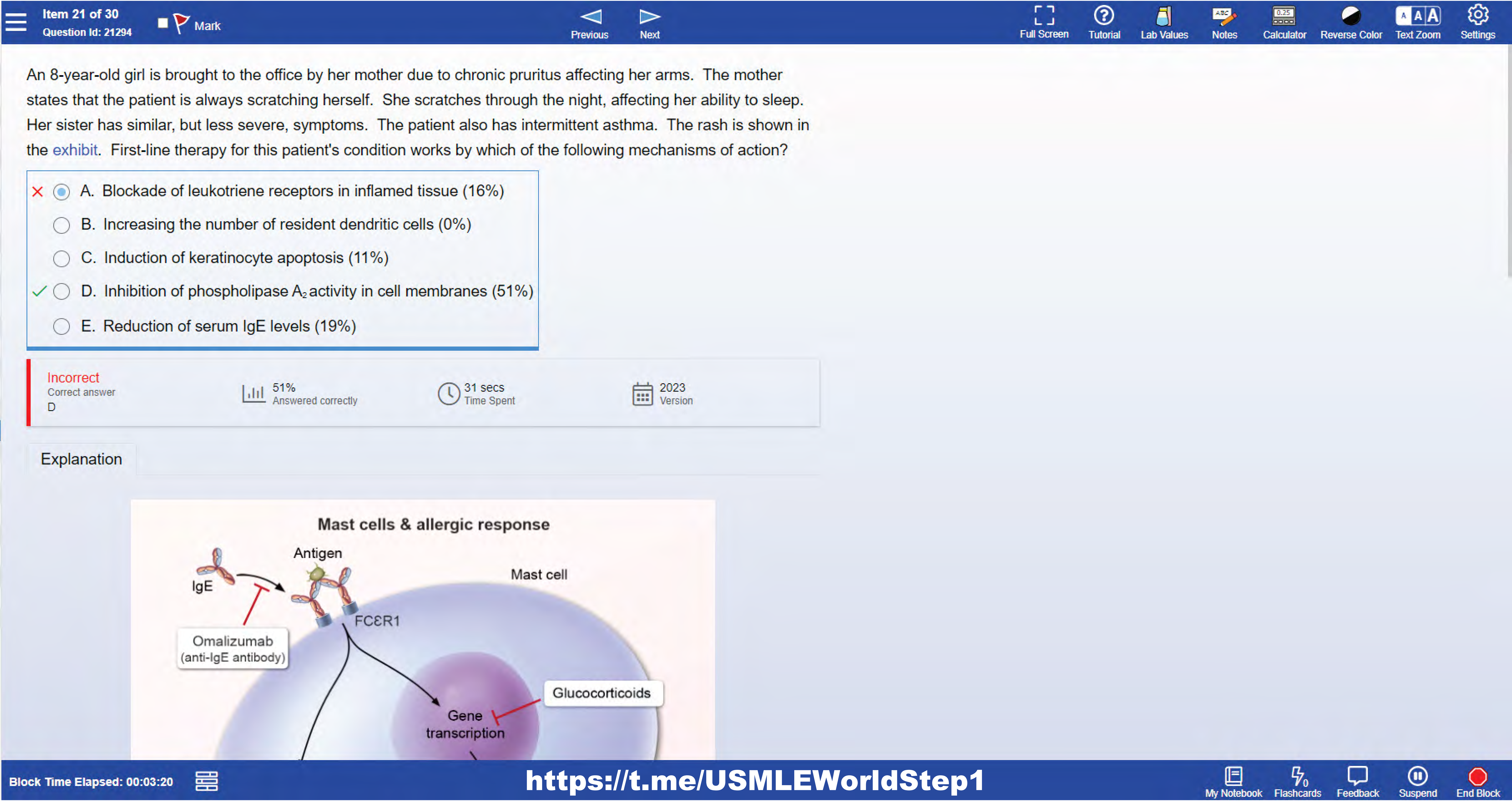
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- ✗ ● A. Blockade of leukotriene receptors in inflamed tissue (16%)
- ○ B. Increasing the number of resident dendritic cells (0%)
- ○ C. Induction of keratinocyte apoptosis (11%)
- ✓ ○ D. Inhibition of phospholipase A_2 activity in cell membranes (51%)
- ○ E. Reduction of serum IgE levels (19%)

Incorrect
Correct answer
D

51%
Answered correctly

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Explanation

Mast cells & allergic response
Antigen
IgE
Mast cell
FCεR1
Omalizumab
(anti-IgE antibody)
Glucocorticoids
Gene
transcription

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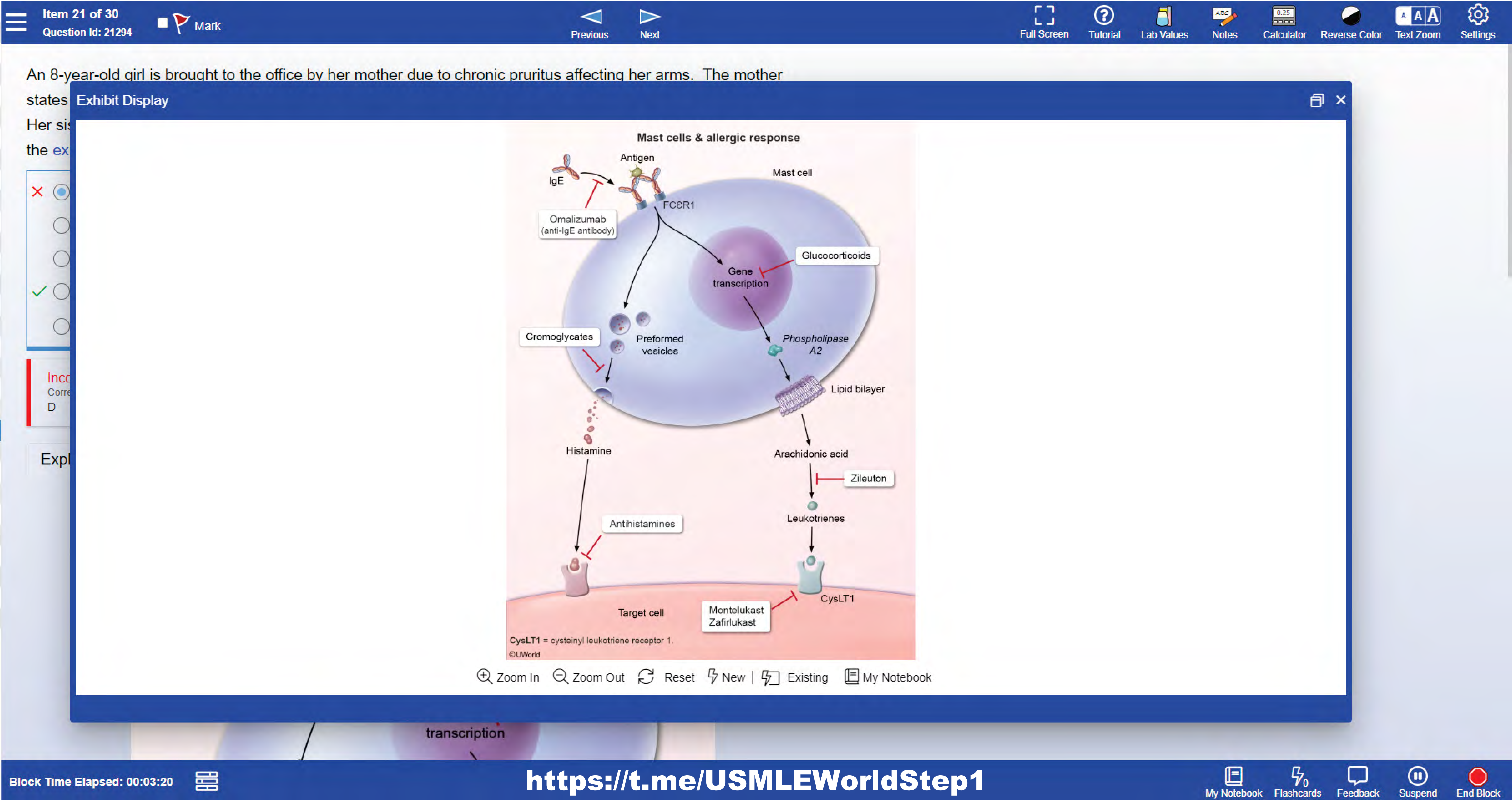
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Mast cells & allergic response
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(anti-IgE antibody)
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Cromoglycates
Preformed
vesicles
Phospholipase
A2
Lipid bilayer
Histamine
Arachidonic acid
Zileuton
Leukotrienes
Antihistamines
CysLT1
Target cell
Montelukast
Zafirlukast
CysLT1 = cysteinyl leukotriene receptor 1.
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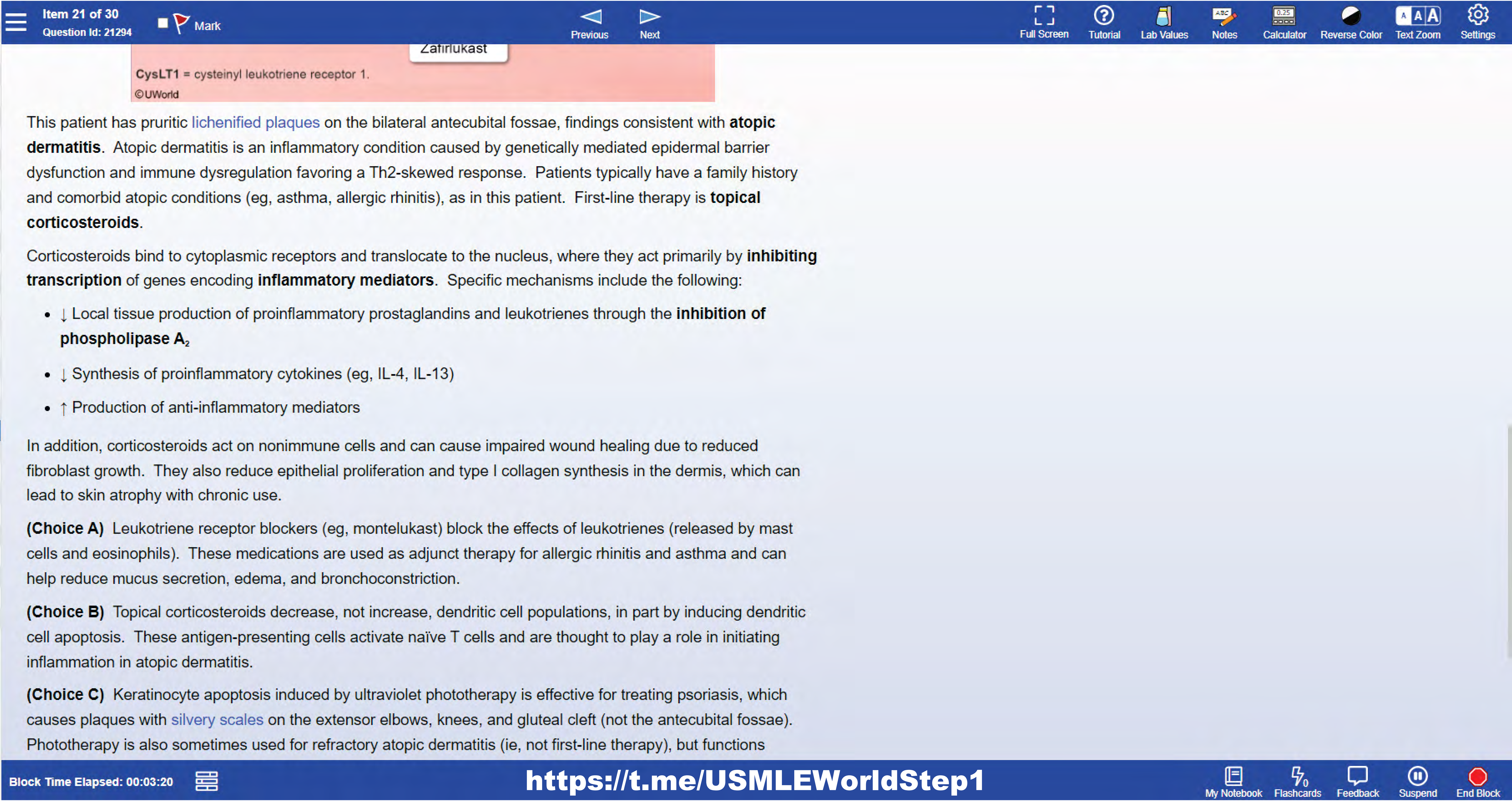

CysLT1 = cysteinyl leukotriene receptor 1.

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This patient has pruritic lichenified plaques on the bilateral antecubital fossae, findings consistent with **atopic dermatitis**. Atopic dermatitis is an inflammatory condition caused by genetically mediated epidermal barrier dysfunction and immune dysregulation favoring a Th2-skewed response. Patients typically have a family history and comorbid atopic conditions (eg, asthma, allergic rhinitis), as in this patient. First-line therapy is **topical corticosteroids**.

Corticosteroids bind to cytoplasmic receptors and translocate to the nucleus, where they act primarily by **inhibiting transcription** of genes encoding **inflammatory mediators**. Specific mechanisms include the following:

- ↓ Local tissue production of proinflammatory prostaglandins and leukotrienes through the **inhibition of phospholipase A_2**
- ↓ Synthesis of proinflammatory cytokines (eg, IL-4, IL-13)
- ↑ Production of anti-inflammatory mediators

In addition, corticosteroids act on nonimmune cells and can cause impaired wound healing due to reduced fibroblast growth. They also reduce epithelial proliferation and type I collagen synthesis in the dermis, which can lead to skin atrophy with chronic use.

(Choice A) Leukotriene receptor blockers (eg, montelukast) block the effects of leukotrienes (released by mast cells and eosinophils). These medications are used as adjunct therapy for allergic rhinitis and asthma and can help reduce mucus secretion, edema, and bronchoconstriction.

(Choice B) Topical corticosteroids decrease, not increase, dendritic cell populations, in part by inducing dendritic cell apoptosis. These antigen-presenting cells activate naïve T cells and are thought to play a role in initiating inflammation in atopic dermatitis.

(Choice C) Keratinocyte apoptosis induced by ultraviolet phototherapy is effective for treating psoriasis, which causes plaques with silvery scales on the extensor elbows, knees, and gluteal cleft (not the antecubital fossae). Phototherapy is also sometimes used for refractory atopic dermatitis (ie, not first-line therapy), but functions

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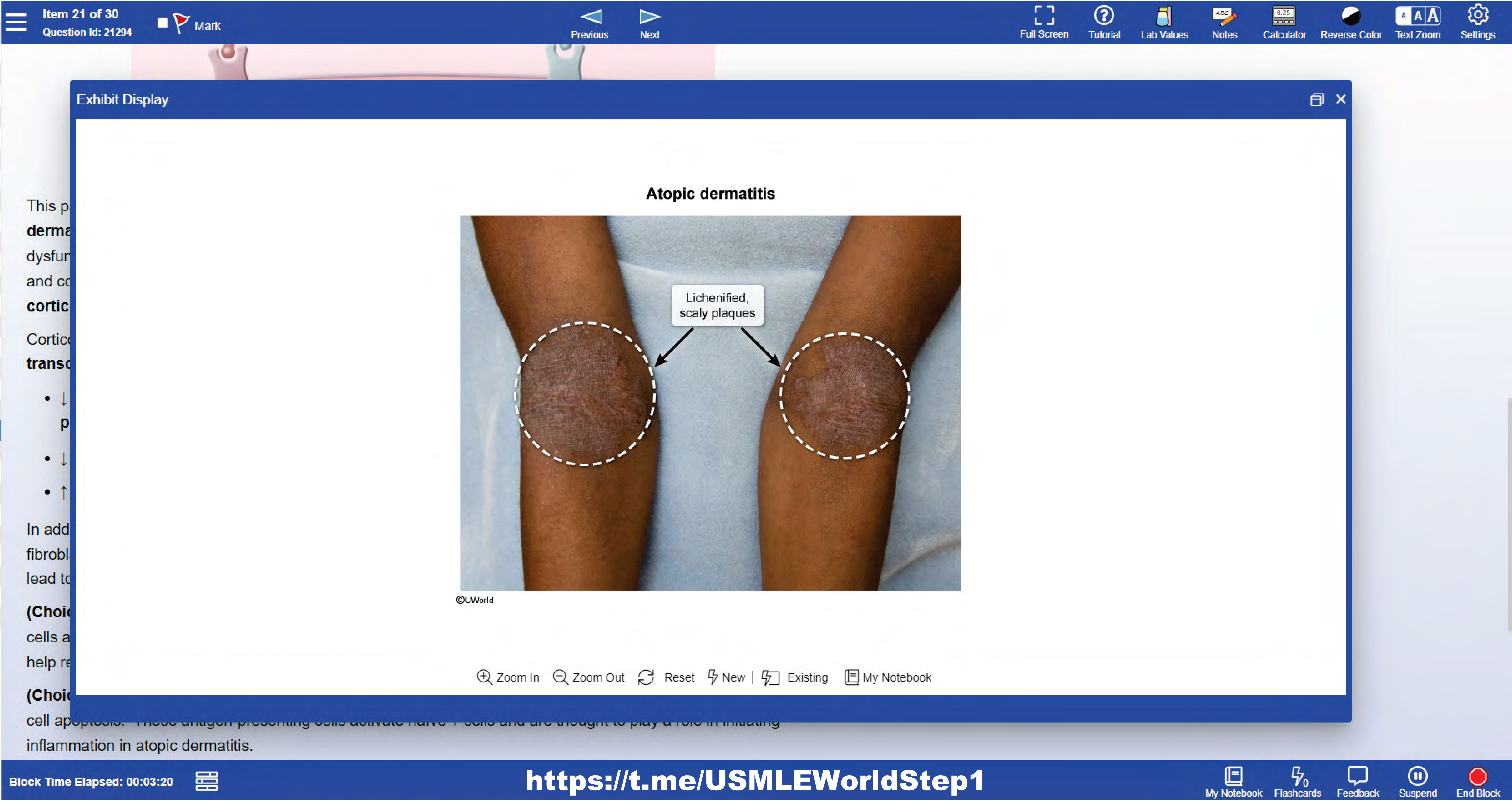
(Choice E) IL-4 normally stimulates B-cell production of IgE and is suppressed with topical corticosteroids. However, corticosteroids also increase CD40-ligand expression on T cells, which stimulates IgE production to a greater degree than IL-4 suppression, and the net effect is a rise in IgE.

Educational objective:
Topical corticosteroids are the first-line therapy for atopic dermatitis. Their mechanism of action includes decreasing tissue production of proinflammatory prostaglandins and leukotrienes through the inhibition of phospholipase A_2; they also inhibit transcription of many other proinflammatory mediators.

Pharmacology Allergy & Immunology Atopic dermatitis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Atopic dermatitis

Lichenified, scaly plaques

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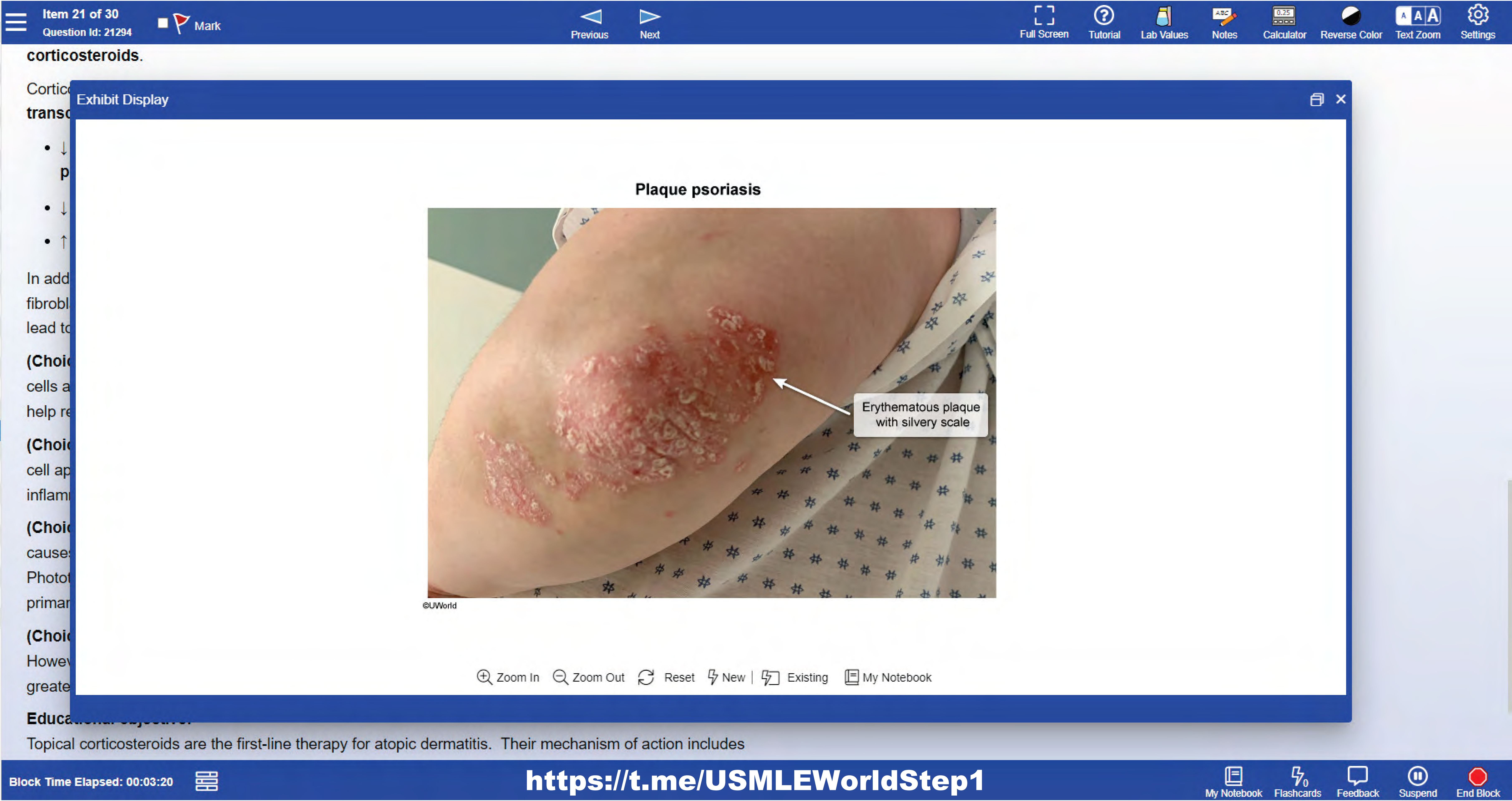
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Erythematous plaque with silvery scale

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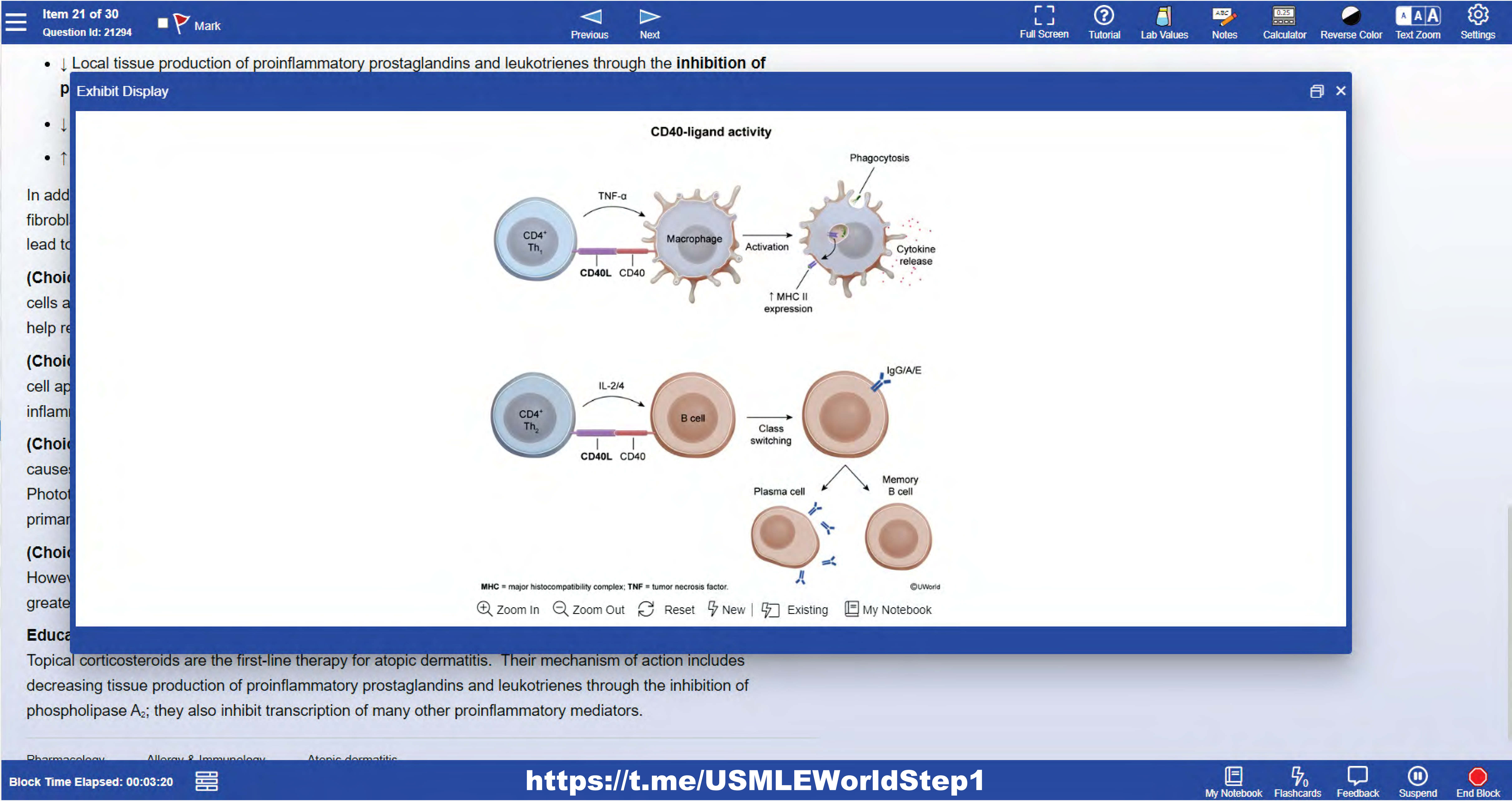
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CD40-ligand activity

Phagocytosis
TNF-α
CD4+ Th1
Macrophage
Activation
Cytokine release
CD40L
CD40
↑ MHC II expression
IgG/A/E
IL-2/4
CD4+ Th2
B cell
Class switching
CD40L
CD40
Plasma cell
Memory B cell

MHC = major histocompatibility complex; **TNF** = tumor necrosis factor.

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Pharmacology Allergy & Immunology Atopic dermatitis

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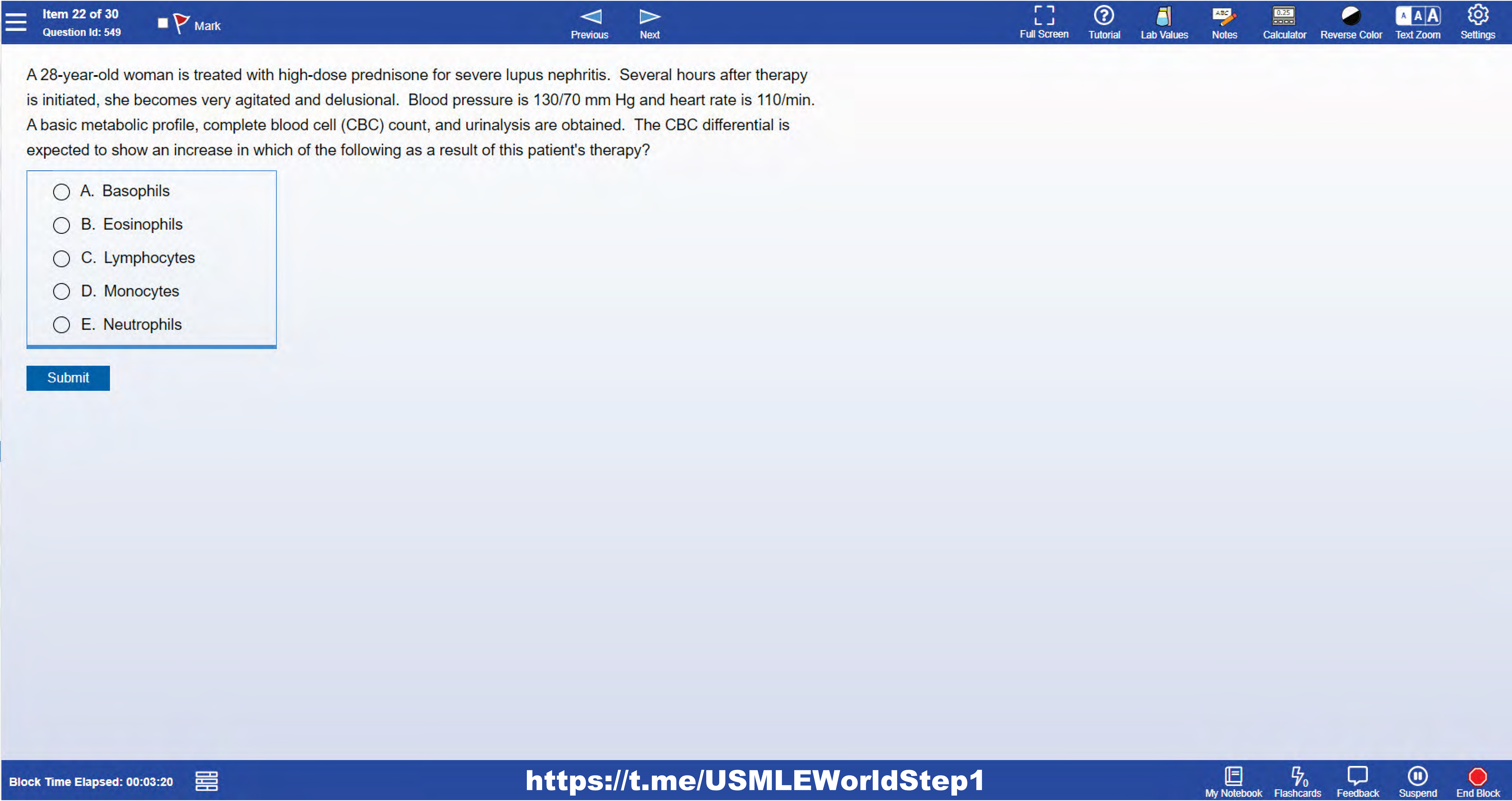
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Question Id: 549

A 28-year-old woman is treated with high-dose prednisone for severe lupus nephritis. Several hours after therapy is initiated, she becomes very agitated and delusional. Blood pressure is 130/70 mm Hg and heart rate is 110/min. A basic metabolic profile, complete blood cell (CBC) count, and urinalysis are obtained. The CBC differential is expected to show an increase in which of the following as a result of this patient's therapy?

○ A. Basophils
○ B. Eosinophils
○ C. Lymphocytes
○ D. Monocytes
○ E. Neutrophils

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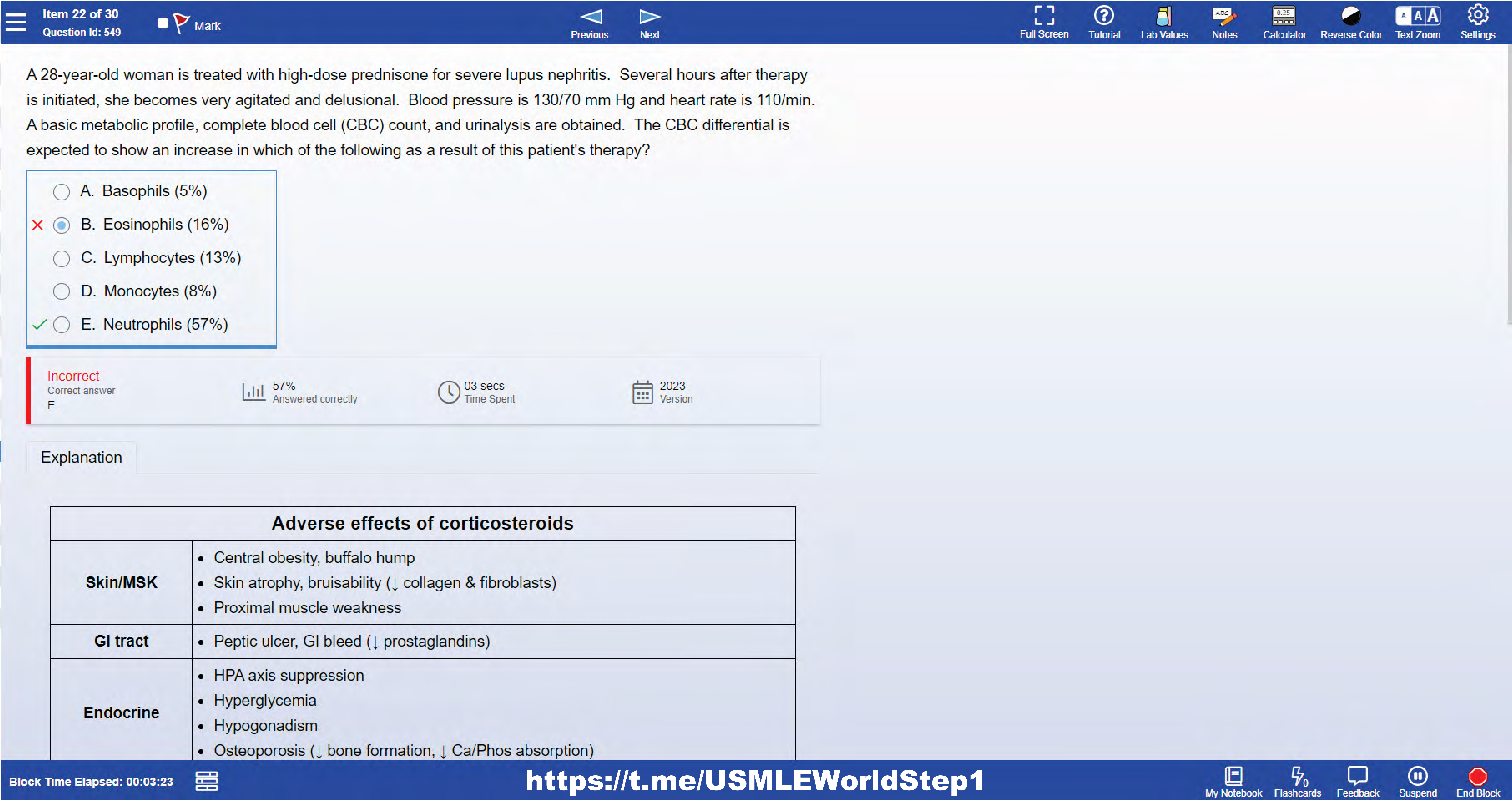
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- ○ A. Basophils (5%)
- ✗ ● B. Eosinophils (16%)
- ○ C. Lymphocytes (13%)
- ○ D. Monocytes (8%)
- ✓ ○ E. Neutrophils (57%)

Incorrect
Correct answer
E

57%
Answered correctly

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Time Spent

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Explanation

Adverse effects of corticosteroids	
Skin/MSK	• Central obesity, buffalo hump • Skin atrophy, bruisability (↓ collagen & fibroblasts) • Proximal muscle weakness
GI tract	• Peptic ulcer, GI bleed (↓ prostaglandins)
Endocrine	• HPA axis suppression • Hyperglycemia • Hypogonadism • Osteoporosis (↓ bone formation, ↓ Ca/Phos absorption)

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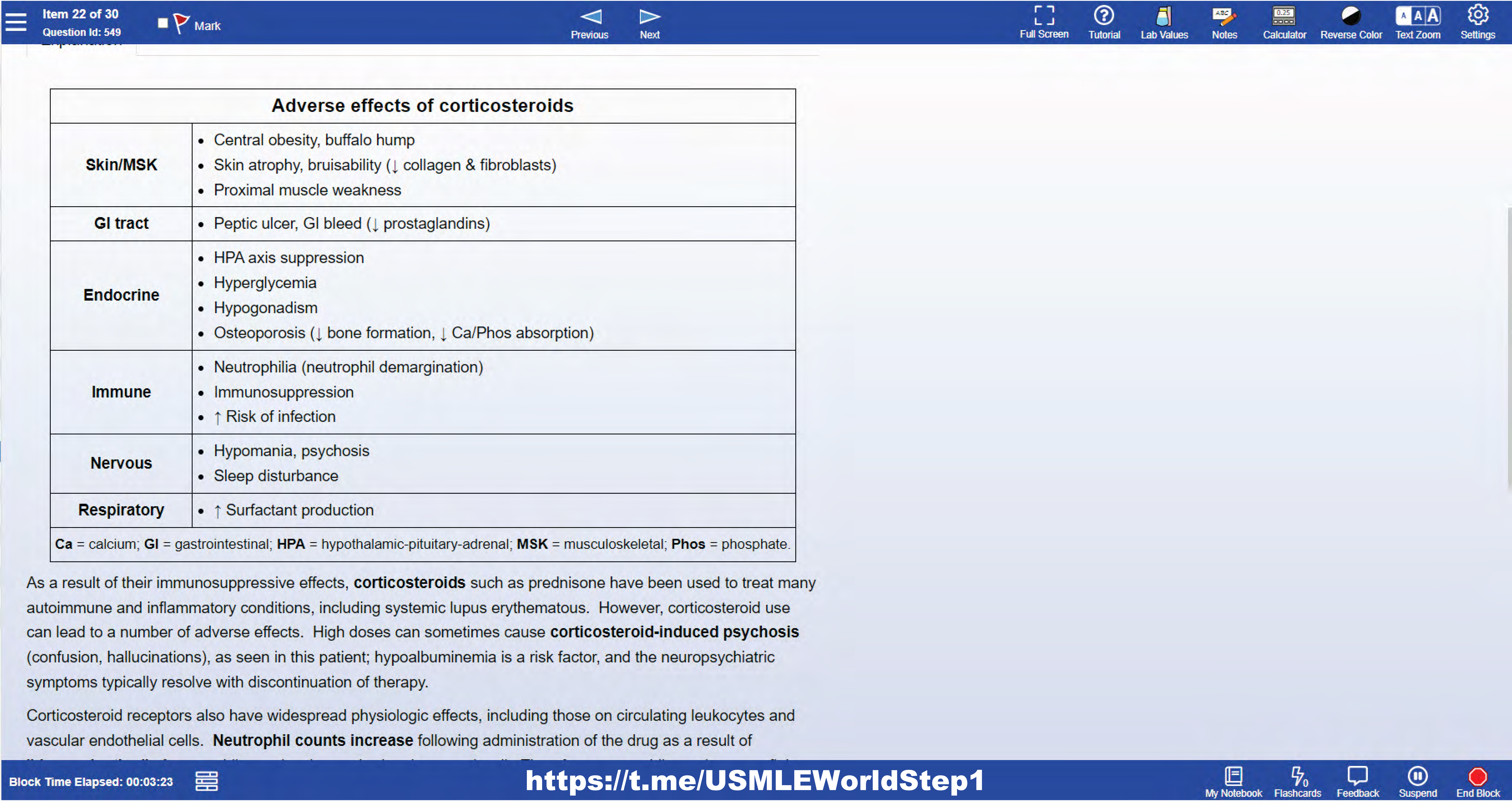
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Endocrine	• HPA axis suppression • Hyperglycemia • Hypogonadism • Osteoporosis (↓ bone formation, ↓ Ca/Phos absorption)
Immune	• Neutrophilia (neutrophil demargination) • Immunosuppression • ↑ Risk of infection
Nervous	• Hypomania, psychosis • Sleep disturbance
Respiratory	• ↑ Surfactant production

Ca = calcium; **GI** = gastrointestinal; **HPA** = hypothalamic-pituitary-adrenal; **MSK** = musculoskeletal; **Phos** = phosphate.

As a result of their immunosuppressive effects, **corticosteroids** such as prednisone have been used to treat many autoimmune and inflammatory conditions, including systemic lupus erythematous. However, corticosteroid use can lead to a number of adverse effects. High doses can sometimes cause **corticosteroid-induced psychosis** (confusion, hallucinations), as seen in this patient; hypoalbuminemia is a risk factor, and the neuropsychiatric symptoms typically resolve with discontinuation of therapy.

Corticosteroid receptors also have widespread physiologic effects, including those on circulating leukocytes and vascular endothelial cells. **Neutrophil counts increase** following administration of the drug as a result of

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Corticosteroid receptors also have widespread physiologic effects, including those on circulating leukocytes and vascular endothelial cells. **Neutrophil counts increase** following administration of the drug as a result of **"demargination"** of neutrophils previously attached to the vessel wall. Therefore, neutrophil recruitment to fight infection in tissues is decreased, potentially contributing to increased infection risk.

(Choice A) Corticosteroids reduce basophil count, which decreases local inflammatory responses by preventing histamine release.

(Choice B) Eosinophil counts decrease significantly with administration of corticosteroids (an effect previously used as the basis for a bioassay for corticosteroids). These drugs are used in allergic conditions as they reduce the eosinophil count and therefore the release of mediators from the eosinophils.

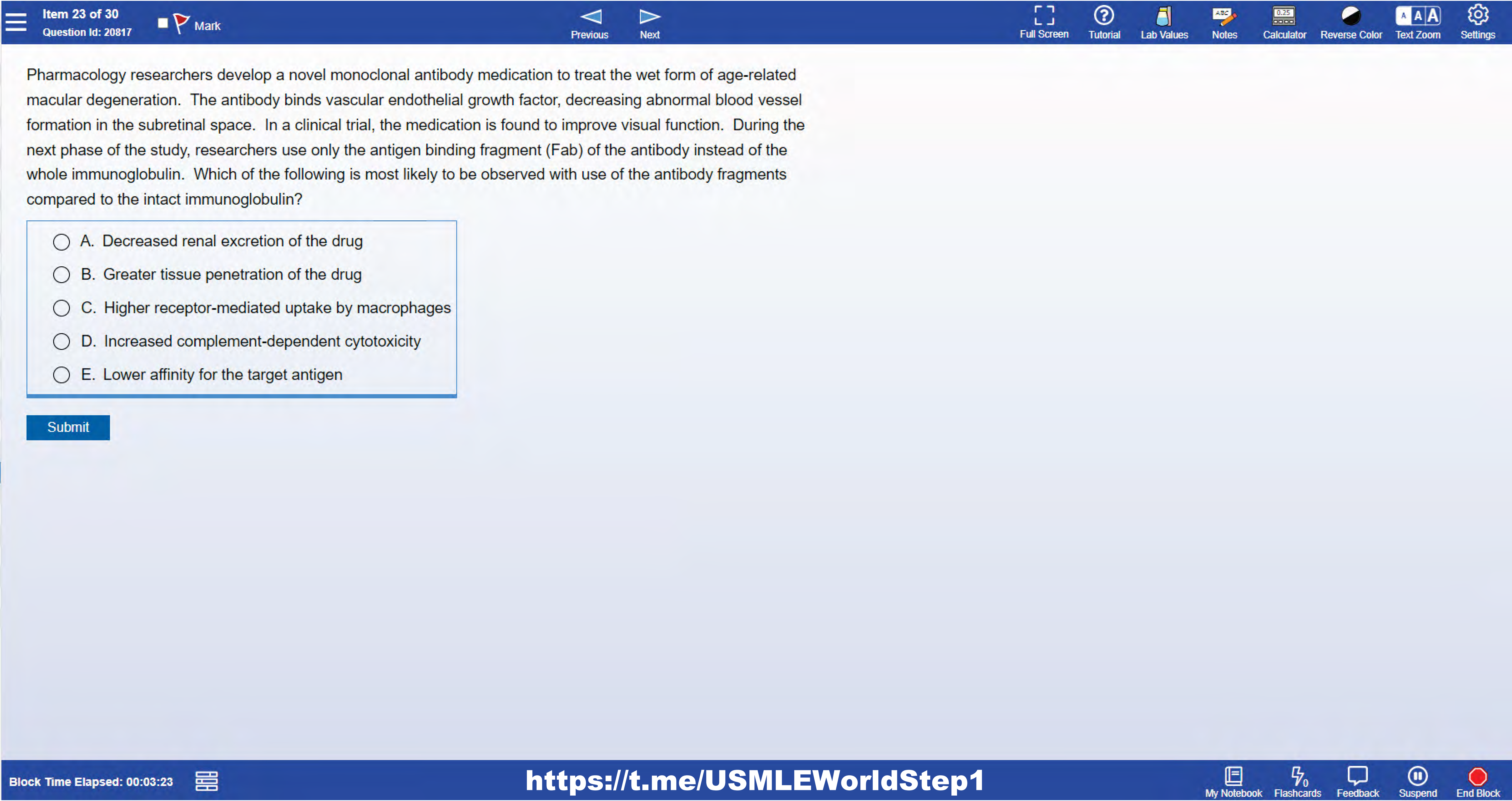
(Choice C) Corticosteroids reduce peripheral lymphocyte counts within minutes as a result of inhibition of immunoglobulin synthesis, stimulation of lymphocyte apoptosis, and lymphocyte redistribution (from the intravascular compartment to the spleen, lymph nodes, and bone marrow). T lymphocyte counts are typically reduced to a greater degree than B lymphocyte counts.

(Choice D) Corticosteroids inhibit peripheral extravasation of monocytes and macrophages and decrease antigen presentation by macrophages and dendritic cells. Blood monocyte levels drop after corticosteroid administration due to redistribution to lymphoid tissues.

Educational objective:

The acute effects of corticosteroids on the white blood cell count include an increased neutrophil count and decreased lymphocyte, monocyte, basophil, and eosinophil counts. The increase in the neutrophil count results from "demargination" of neutrophils previously attached to the vessel wall.

References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Pharmacology researchers develop a novel monoclonal antibody medication to treat the wet form of age-related macular degeneration. The antibody binds vascular endothelial growth factor, decreasing abnormal blood vessel formation in the subretinal space. In a clinical trial, the medication is found to improve visual function. During the next phase of the study, researchers use only the antigen binding fragment (Fab) of the antibody instead of the whole immunoglobulin. Which of the following is most likely to be observed with use of the antibody fragments compared to the intact immunoglobulin?

○ A. Decreased renal excretion of the drug
○ B. Greater tissue penetration of the drug
○ C. Higher receptor-mediated uptake by macrophages
○ D. Increased complement-dependent cytotoxicity
○ E. Lower affinity for the target antigen

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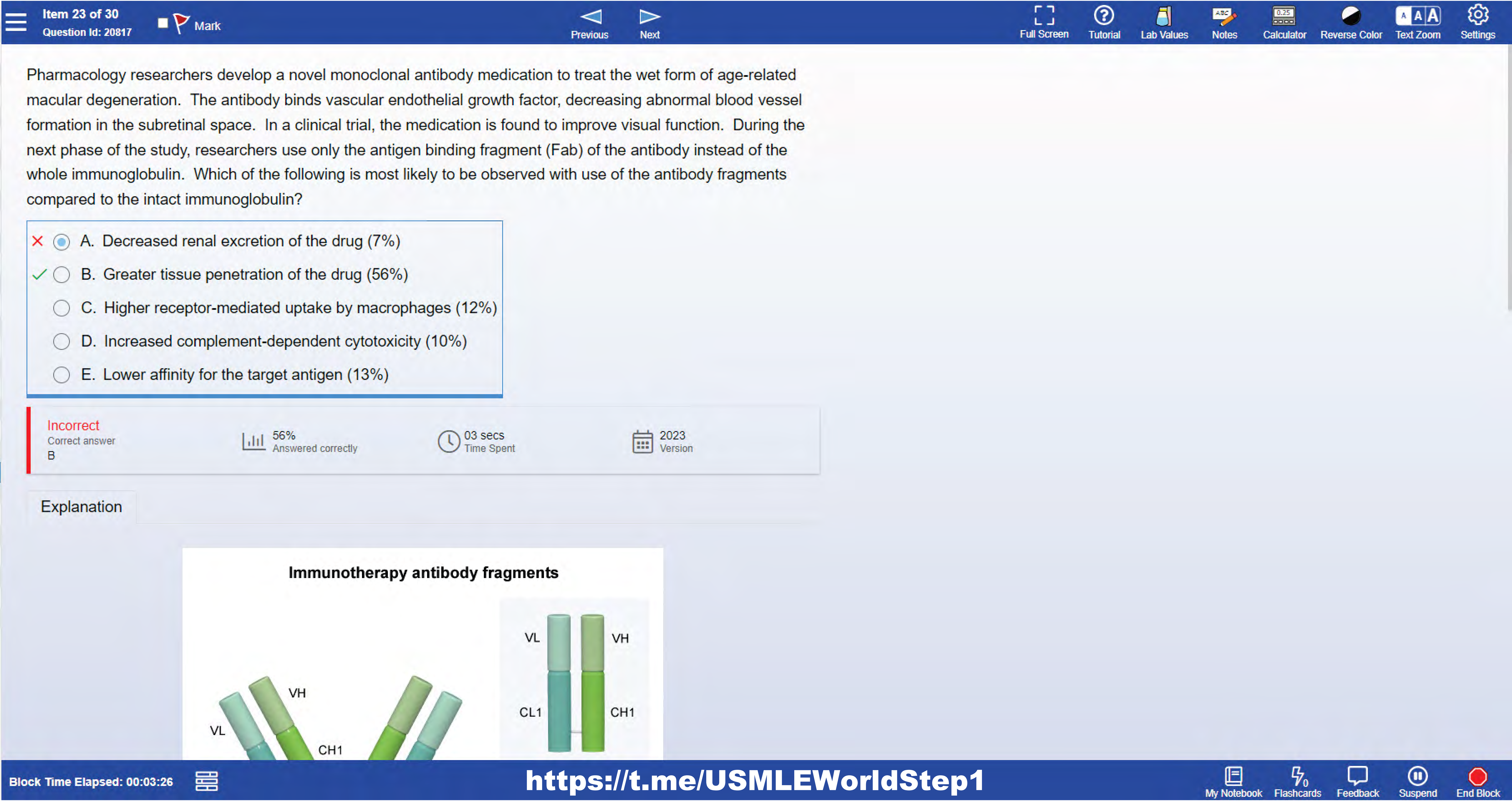
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✗ ● A. Decreased renal excretion of the drug (7%)
✓ ○ B. Greater tissue penetration of the drug (56%)
○ C. Higher receptor-mediated uptake by macrophages (12%)
○ D. Increased complement-dependent cytotoxicity (10%)
○ E. Lower affinity for the target antigen (13%)

Incorrect
Correct answer
B

56%
Answered correctly

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Explanation

Immunotherapy antibody fragments

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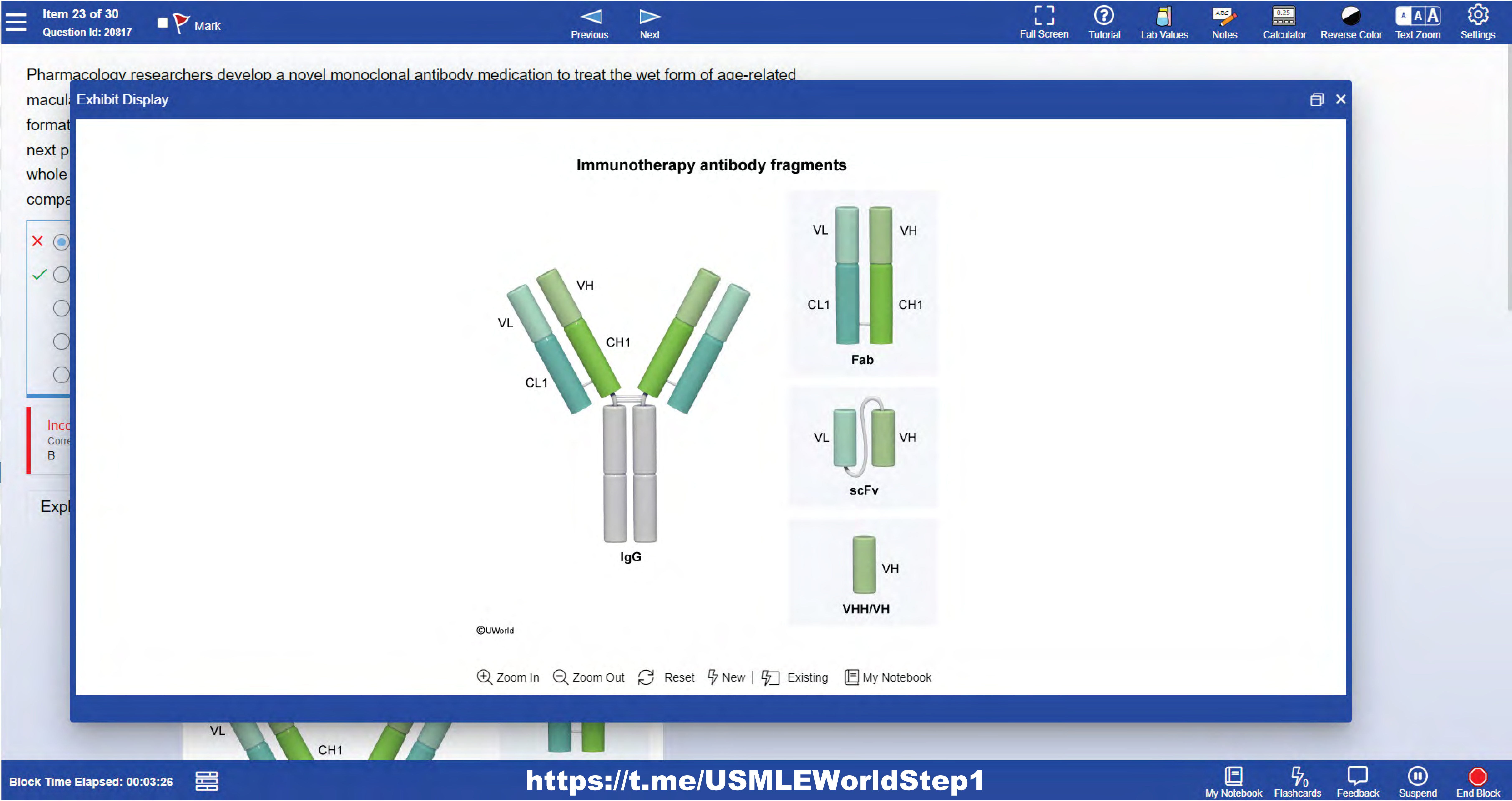
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Immunotherapy antibody fragments

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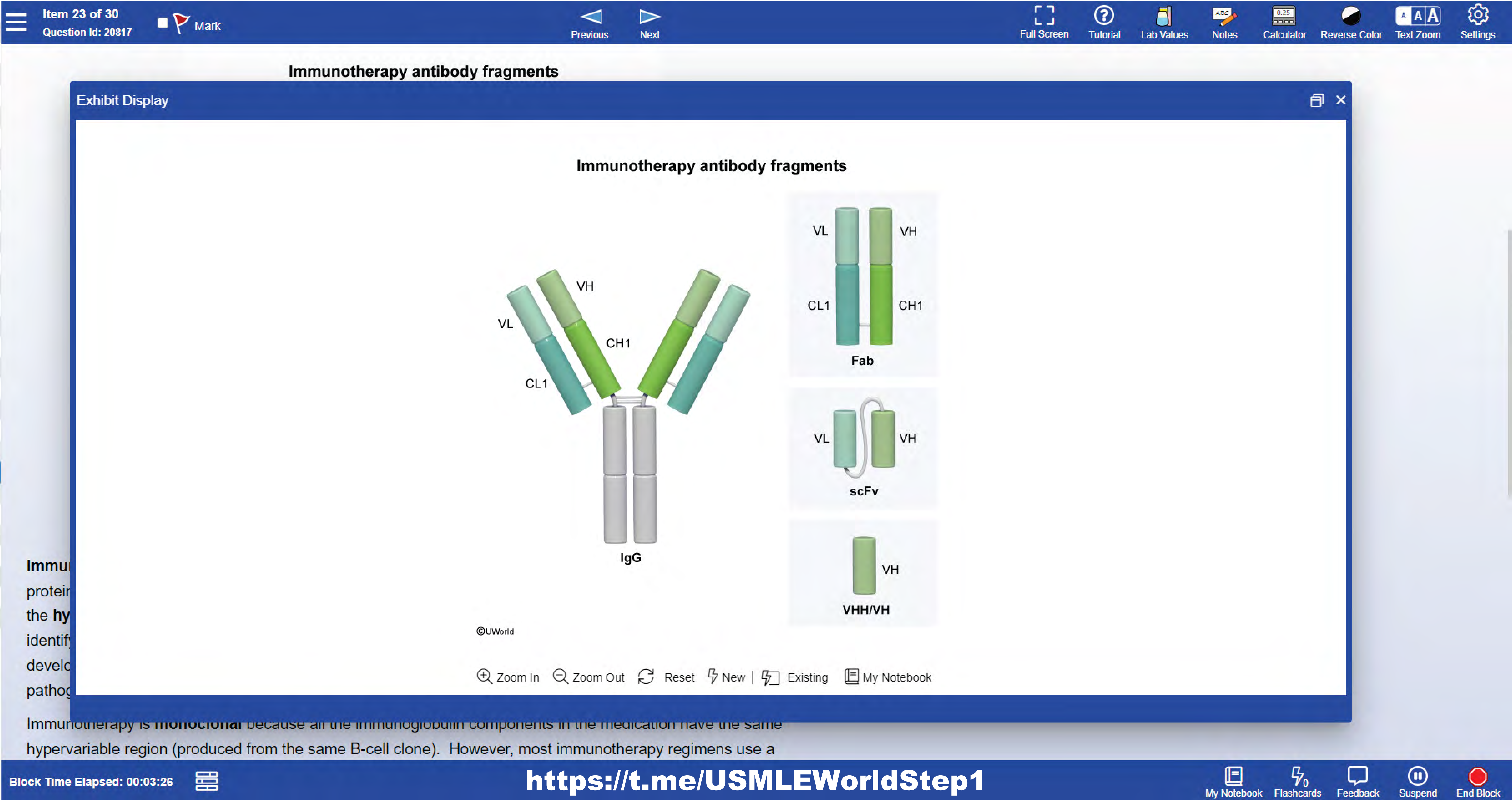
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Immunotherapy antibody fragments

Immunotherapy antibody fragments

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Immunotherapy is **monoclonal** because all the immunoglobulin components in the medication have the same hypervariable region (produced from the same B-cell clone). However, most immunotherapy regimens use a

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Immunoglobulins (antibodies) are the principal component of the humoral immune system. They are effector proteins that bind to specific **epitopes of antigens** based on the unique group of 110-130 amino acids present in the **hypervariable region** of the immunoglobulin light and heavy chain. Because individual immunoglobulins can identify molecular targets with a high degree of specificity, immunoglobulin therapy **(immunotherapy)** has been developed to target specific ligands, cytokines, receptors, growth factors, and other proteins that contribute to the pathogenesis or progression of inflammatory and neoplastic conditions.

Immunotherapy is **monoclonal** because all the immunoglobulin components in the medication have the same hypervariable region (produced from the same B-cell clone). However, most immunotherapy regimens use a **fragment** of the immunoglobulin with 1 valence (binding) site rather than the full immunoglobulin with 2 valence sites, because fragments are significantly **smaller** than the full immunoglobulin, which improves **tissue/tumor penetration** and medication pharmacokinetics.

Common types of immunoglobulin fragments include the following:

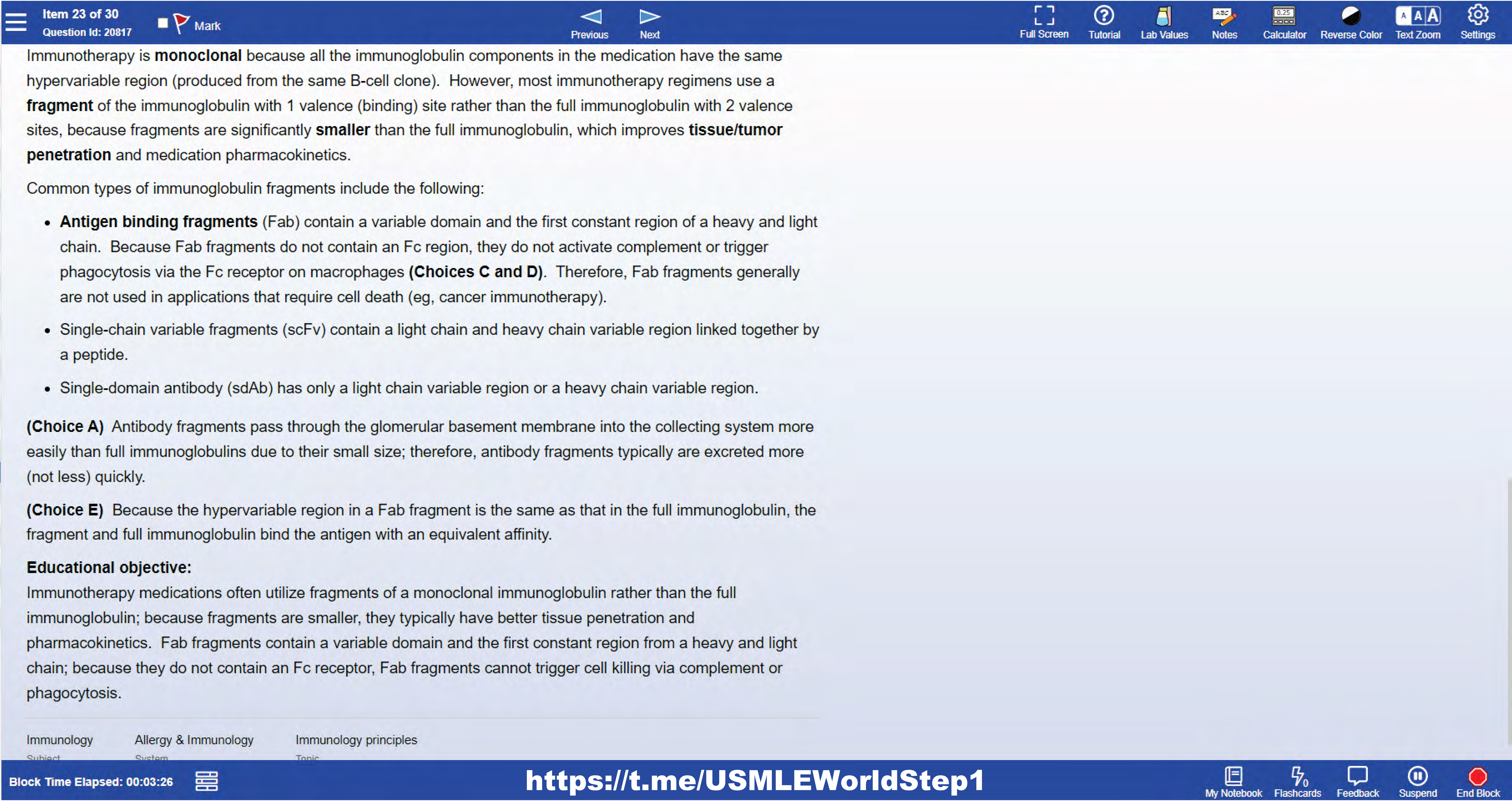
- **Antigen binding fragments** (Fab) contain a variable domain and the first constant region of a heavy and light chain. Because Fab fragments do not contain an Fc region, they do not activate complement or trigger phagocytosis via the Fc receptor on macrophages **(Choices C and D)**. Therefore, Fab fragments generally are not used in applications that require cell death (eg, cancer immunotherapy).
- Single-chain variable fragments (scFv) contain a light chain and heavy chain variable region linked together by a peptide.
- Single-domain antibody (sdAb) has only a light chain variable region or a heavy chain variable region.

(Choice A) Antibody fragments pass through the glomerular basement membrane into the collecting system more easily than full immunoglobulins due to their small size; therefore, antibody fragments typically are excreted more (not less) quickly.

(Choice E) Because the hypervariable region in a Fab fragment is the same as that in the full immunoglobulin, the fragment and full immunoglobulin bind the antigen with an equivalent affinity.

Educational objective:

Immunotherapy medications often utilize fragments of a monoclonal immunoglobulin rather than the full



Immunotherapy is **monoclonal** because all the immunoglobulin components in the medication have the same hypervariable region (produced from the same B-cell clone). However, most immunotherapy regimens use a **fragment** of the immunoglobulin with 1 valence (binding) site rather than the full immunoglobulin with 2 valence sites, because fragments are significantly **smaller** than the full immunoglobulin, which improves **tissue/tumor penetration** and medication pharmacokinetics.

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(Choice E) Because the hypervariable region in a Fab fragment is the same as that in the full immunoglobulin, the fragment and full immunoglobulin bind the antigen with an equivalent affinity.

Educational objective:

Immunotherapy medications often utilize fragments of a monoclonal immunoglobulin rather than the full immunoglobulin; because fragments are smaller, they typically have better tissue penetration and pharmacokinetics. Fab fragments contain a variable domain and the first constant region from a heavy and light chain; because they do not contain an Fc receptor, Fab fragments cannot trigger cell killing via complement or phagocytosis.

Immunology	Allergy & Immunology	Immunology principles
Subject	System	Topic

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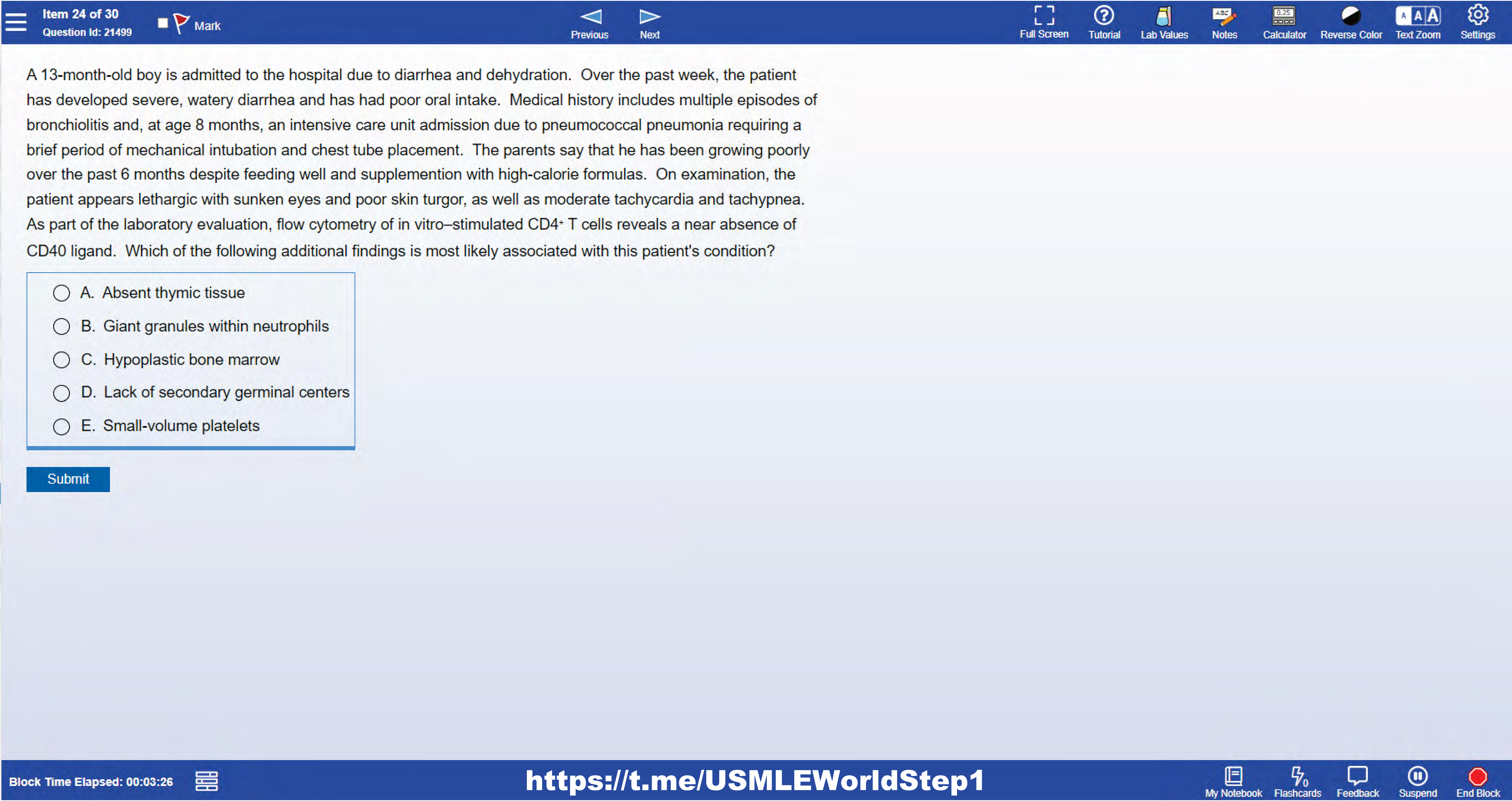
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A 13-month-old boy is admitted to the hospital due to diarrhea and dehydration. Over the past week, the patient has developed severe, watery diarrhea and has had poor oral intake. Medical history includes multiple episodes of bronchiolitis and, at age 8 months, an intensive care unit admission due to pneumococcal pneumonia requiring a brief period of mechanical intubation and chest tube placement. The parents say that he has been growing poorly over the past 6 months despite feeding well and supplemention with high-calorie formulas. On examination, the patient appears lethargic with sunken eyes and poor skin turgor, as well as moderate tachycardia and tachypnea. As part of the laboratory evaluation, flow cytometry of in vitro–stimulated $CD4^+$ T cells reveals a near absence of CD40 ligand. Which of the following additional findings is most likely associated with this patient's condition?

○ A. Absent thymic tissue

○ B. Giant granules within neutrophils

○ C. Hypoplastic bone marrow

○ D. Lack of secondary germinal centers

○ E. Small-volume platelets

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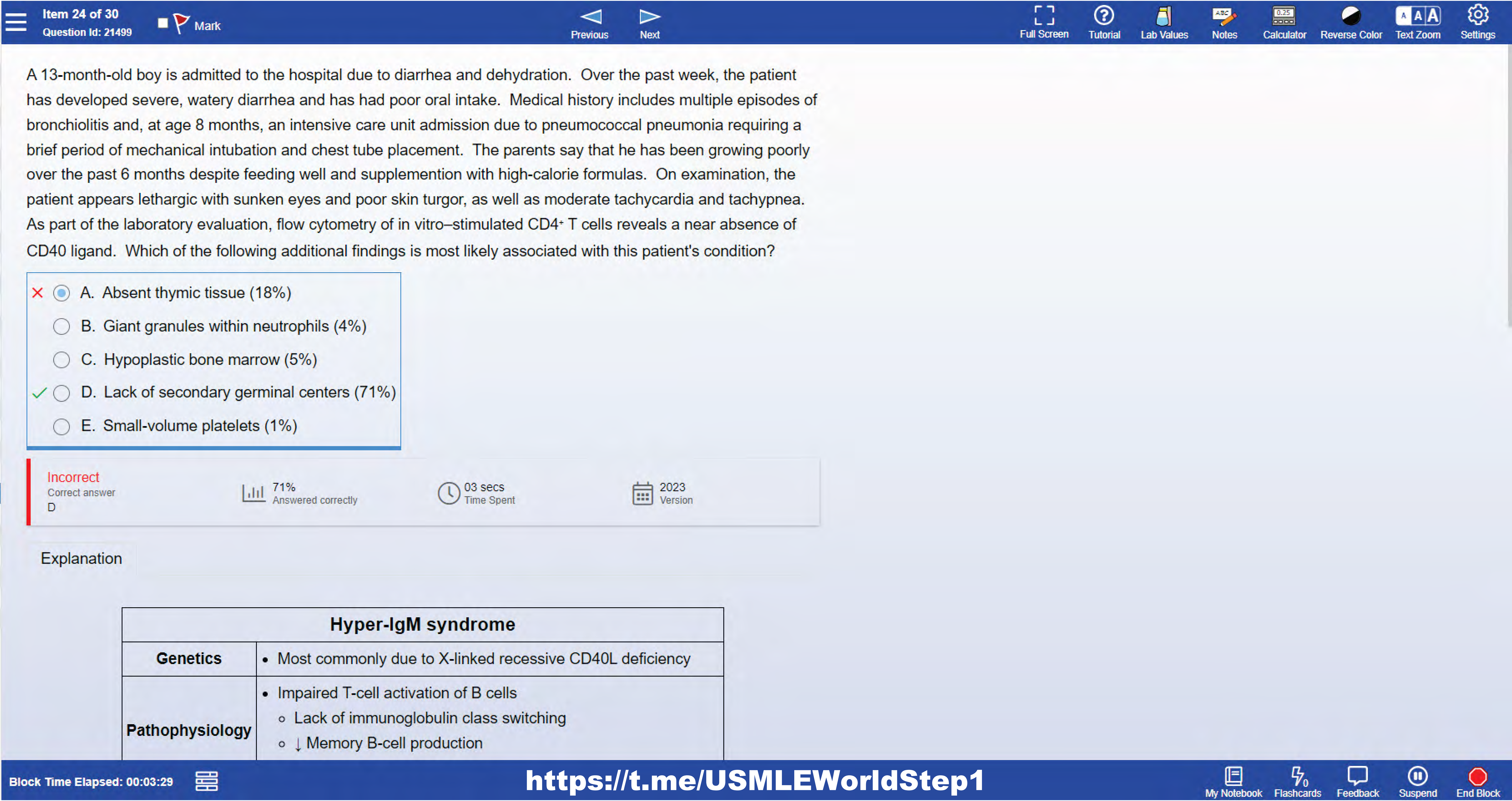
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✗ ● A. Absent thymic tissue (18%)

○ B. Giant granules within neutrophils (4%)

○ C. Hypoplastic bone marrow (5%)

✓ ○ D. Lack of secondary germinal centers (71%)

○ E. Small-volume platelets (1%)

Incorrect
Correct answer
D

71%
Answered correctly

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Explanation

Hyper-IgM syndrome	
Genetics	• Most commonly due to X-linked recessive CD40L deficiency
Pathophysiology	• Impaired T-cell activation of B cells ∘ Lack of immunoglobulin class switching ∘ ↓ Memory B-cell production

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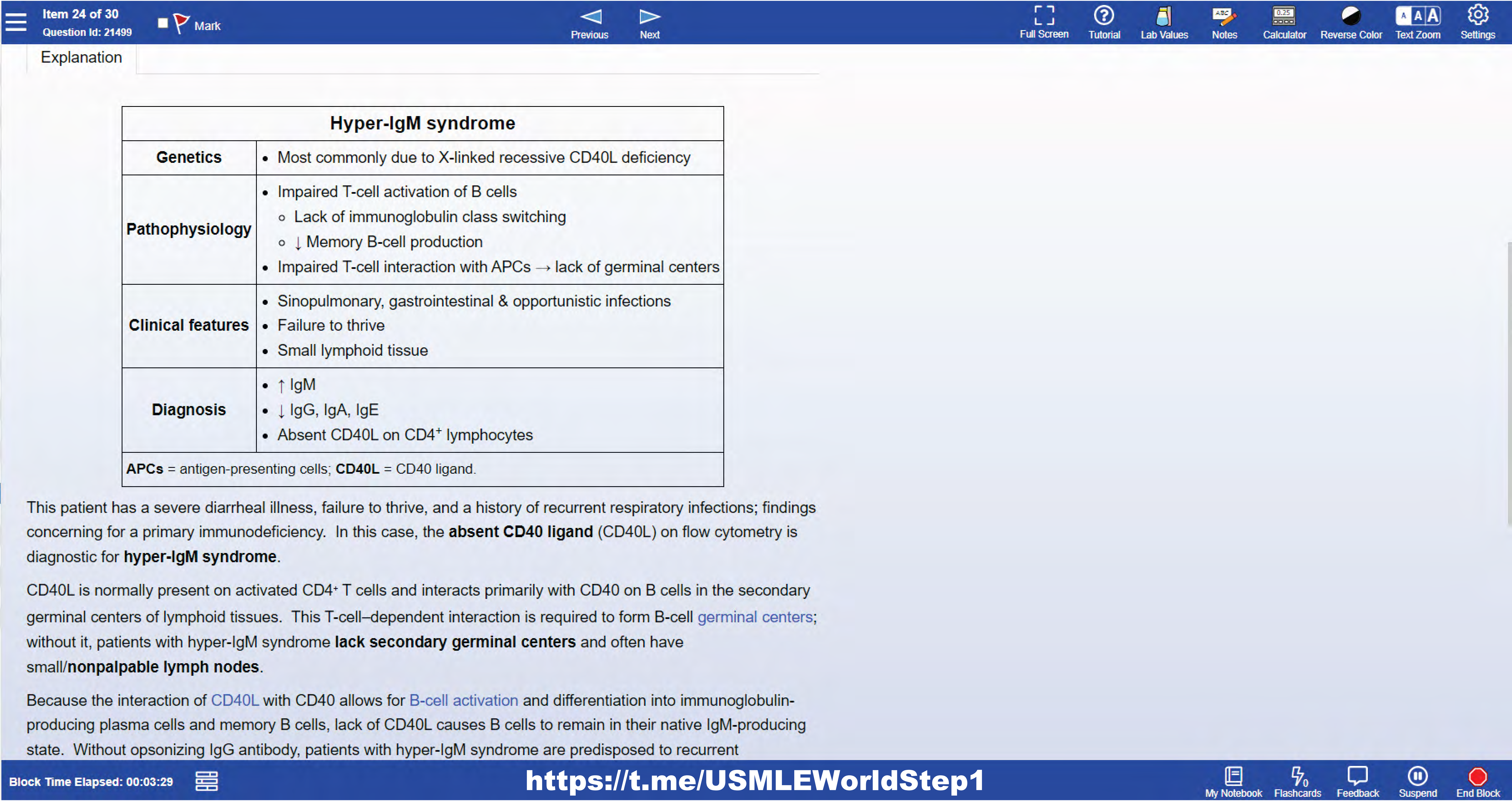
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Explanation

Hyper-IgM syndrome	
Genetics	• Most commonly due to X-linked recessive CD40L deficiency
Pathophysiology	• Impaired T-cell activation of B cells ∘ Lack of immunoglobulin class switching ∘ ↓ Memory B-cell production • Impaired T-cell interaction with APCs → lack of germinal centers
Clinical features	• Sinopulmonary, gastrointestinal & opportunistic infections • Failure to thrive • Small lymphoid tissue
Diagnosis	• ↑ IgM • ↓ IgG, IgA, IgE • Absent CD40L on CD4$^+$ lymphocytes
APCs = antigen-presenting cells; **CD40L** = CD40 ligand.	

This patient has a severe diarrheal illness, failure to thrive, and a history of recurrent respiratory infections; findings concerning for a primary immunodeficiency. In this case, the **absent CD40 ligand** (CD40L) on flow cytometry is diagnostic for **hyper-IgM syndrome**.

CD40L is normally present on activated CD4$^+$ T cells and interacts primarily with CD40 on B cells in the secondary germinal centers of lymphoid tissues. This T-cell–dependent interaction is required to form B-cell germinal centers; without it, patients with hyper-IgM syndrome **lack secondary germinal centers** and often have small/**nonpalpable lymph nodes**.

Because the interaction of CD40L with CD40 allows for B-cell activation and differentiation into immunoglobulin-producing plasma cells and memory B cells, lack of CD40L causes B cells to remain in their native IgM-producing state. Without opsonizing IgG antibody, patients with hyper-IgM syndrome are predisposed to recurrent

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without it, patients with hyper-IgM syndrome **lack secondary germinal centers** and often have small/**nonpalpable lymph nodes**.

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(Choice A) Absent thymic tissue, which can be seen in DiGeorge syndrome, results in absent T-cell production. T-cell deficiency presents with opportunistic infections and failure to thrive in infancy but would be associated with absence of CD4$^+$ T cells themselves (not just CD40L).

(Choice B) Giant granules within neutrophils is a pathognomonic finding for Chédiak-Higashi syndrome, a condition caused by impaired intracellular trafficking of vesicles (eg, lysosomes, melanosomes). In addition to pyogenic infections, patients typically have oculocutaneous albinism and neurologic dysfunction.

(Choice C) Hypoplastic bone marrow is seen with aplastic anemia. Recurrent infections occur due to the absence of leukocyte production, but signs of anemia (eg, fatigue, pallor) and thrombocytopenia (eg, bleeding, bruising) are also typically present.

(Choice E) Small-volume platelets are characteristic of Wiskott-Aldrich syndrome, in which a defect in the leukocyte cytoskeleton leads to recurrent infections.

Educational objective:

Hyper-IgM syndrome presents with recurrent sinopulmonary and gastrointestinal infections due to the absence of CD40 ligand on CD4$^+$ T cells. Lack of interaction between CD40L and CD40 on B cells prevents the development of secondary germinal centers and impairs B-cell activation and immunoglobulin class switching.

Immunology	Allergy & Immunology	Hyper-igm syndrome
Subject	System	Topic

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Clinical features	- Sinopulmonary, gastrointestinal & opportunistic infections - Failure to thrive

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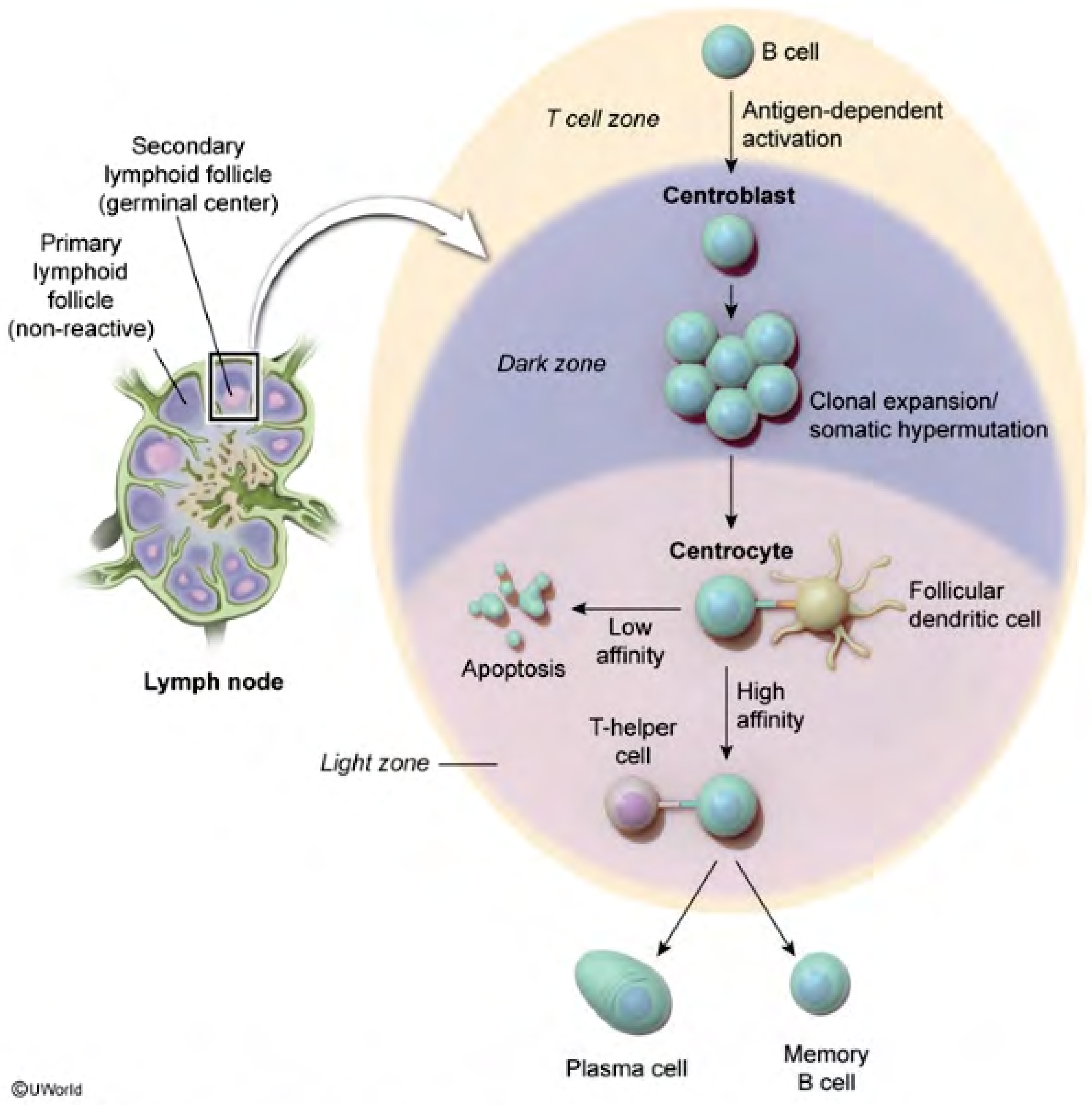
Germinal center reaction


B cell
T cell zone
Antigen-dependent activation
Centroblast
Secondary lymphoid follicle (germinal center)
Primary lymphoid follicle (non-reactive)
Dark zone
Clonal expansion/ somatic hypermutation
Centrocyte
Follicular dendritic cell
Low affinity
Apoptosis
High affinity
T-helper cell
Light zone
Lymph node
Plasma cell
Memory B cell
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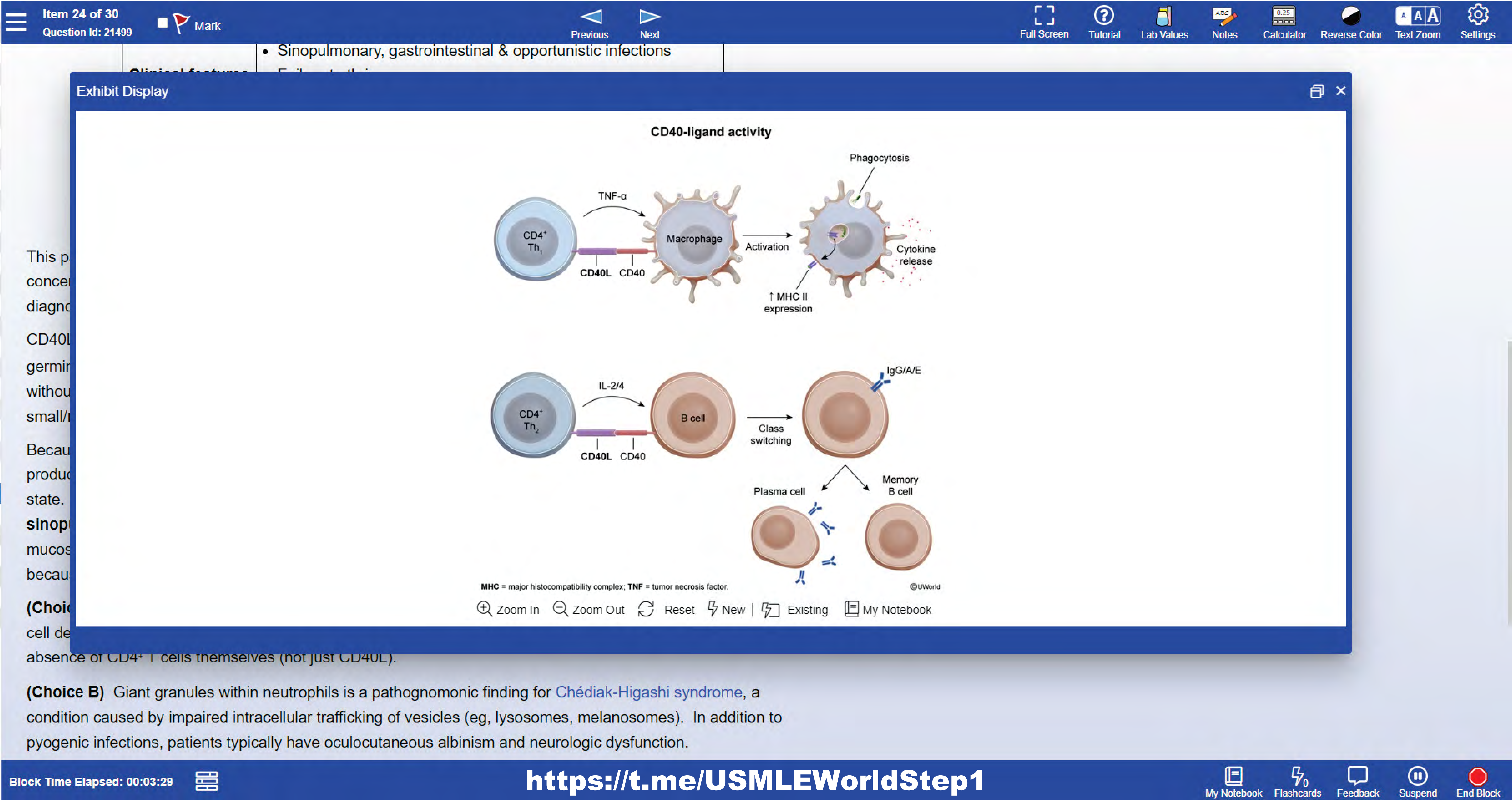
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Phagocytosis
TNF-α
CD4+ Th1
Macrophage
Activation
Cytokine release
CD40L
CD40
↑ MHC II expression
IgG/A/E
IL-2/4
CD4+ Th2
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Class switching
Plasma cell
Memory B cell
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- Sinopulmonary, gastrointestinal & opportunistic infections

CD40-ligand activity

MHC = major histocompatibility complex; **TNF** = tumor necrosis factor.

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absence of CD4+ T cells themselves (not just CD40L).

(Choice B) Giant granules within neutrophils is a pathognomonic finding for Chédiak-Higashi syndrome, a condition caused by impaired intracellular trafficking of vesicles (eg, lysosomes, melanosomes). In addition to pyogenic infections, patients typically have oculocutaneous albinism and neurologic dysfunction.

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APCs = antigen-presenting cells; **CD40L** = CD40 ligand.

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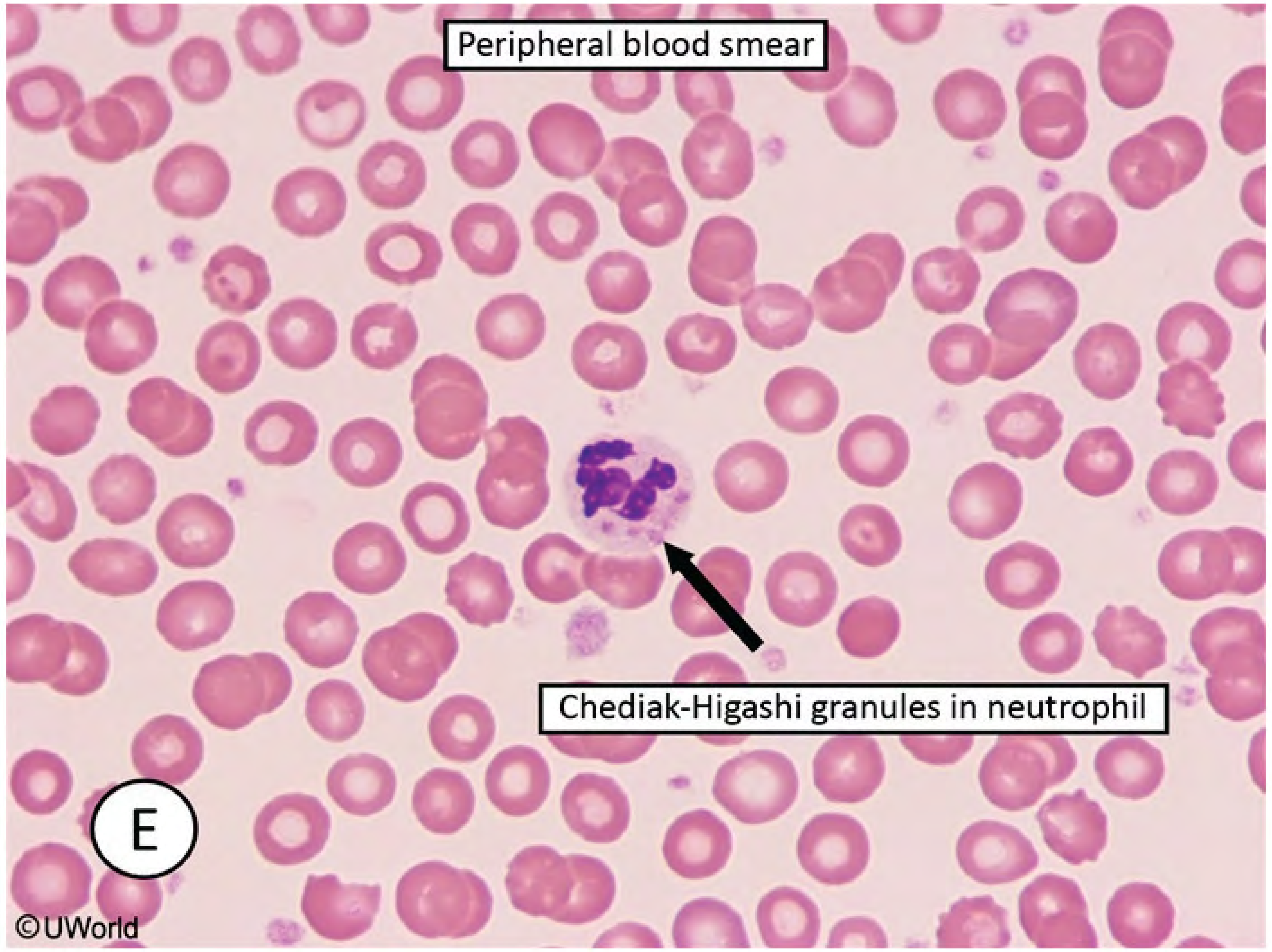
Peripheral blood smear
Chediak-Higashi granules in neutrophil
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(Choice E) Small-volume platelets are characteristic of Wiskott-Aldrich syndrome, in which a defect in the

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diagnostic for **hyper-IgM syndrome**.

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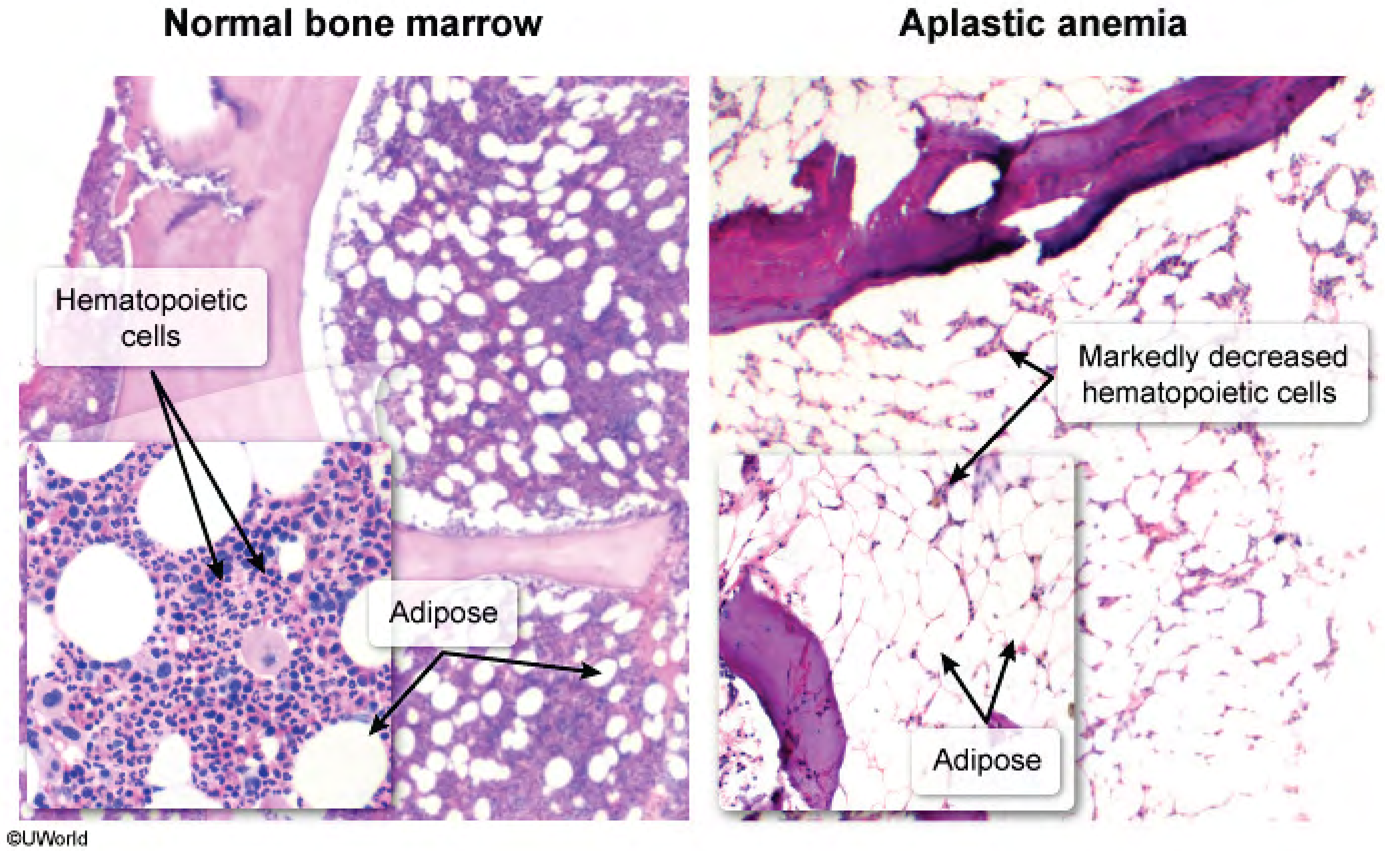
Normal bone marrow
Aplastic anemia
Hematopoietic cells
Adipose
Markedly decreased hematopoietic cells
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Hyper-IgM syndrome presents with recurrent sinopulmonary and gastrointestinal infections due to the absence of

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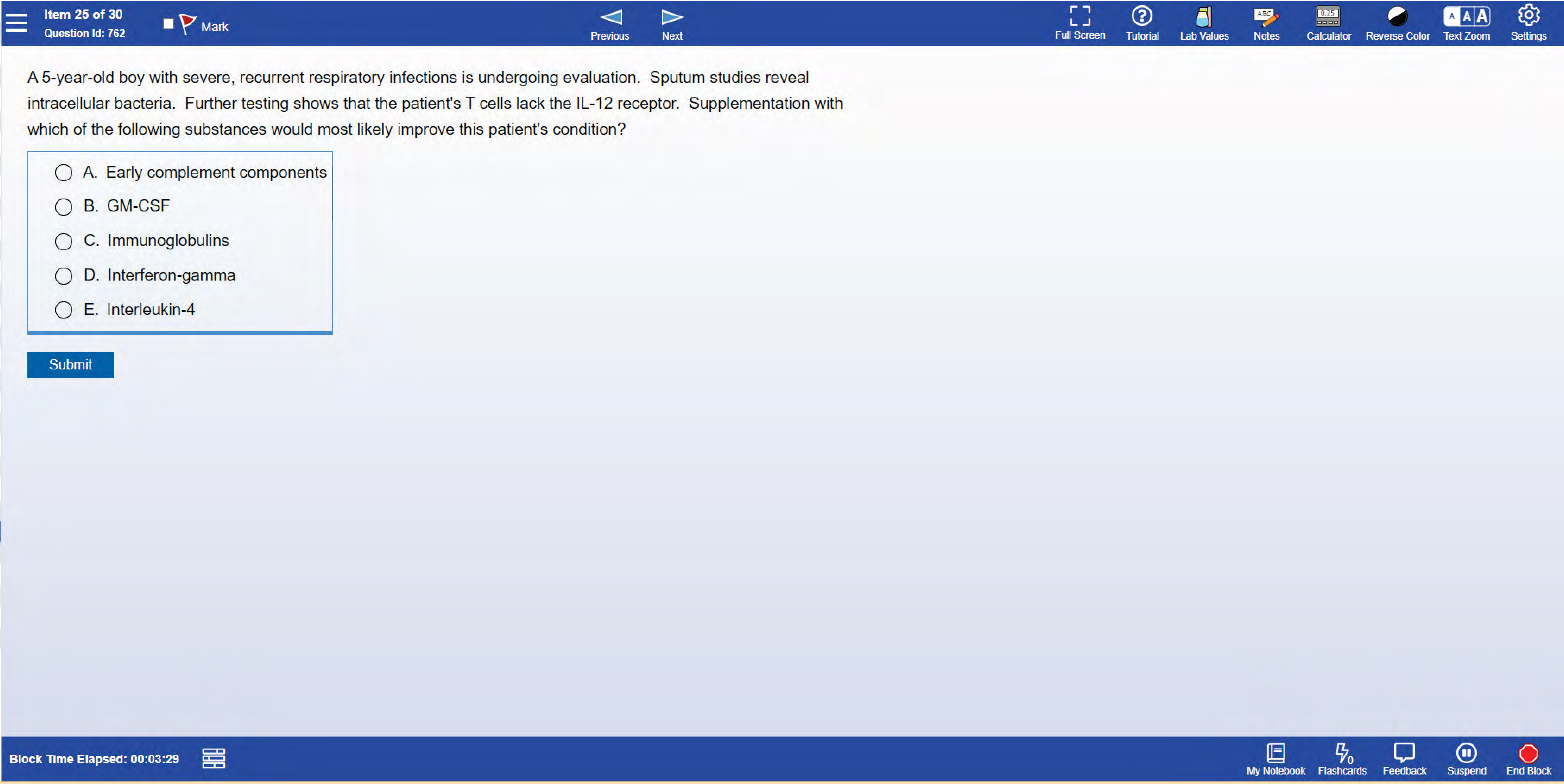
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A 5-year-old boy with severe, recurrent respiratory infections is undergoing evaluation. Sputum studies reveal intracellular bacteria. Further testing shows that the patient's T cells lack the IL-12 receptor. Supplementation with which of the following substances would most likely improve this patient's condition?

○ A. Early complement components
○ B. GM-CSF
○ C. Immunoglobulins
○ D. Interferon-gamma
○ E. Interleukin-4

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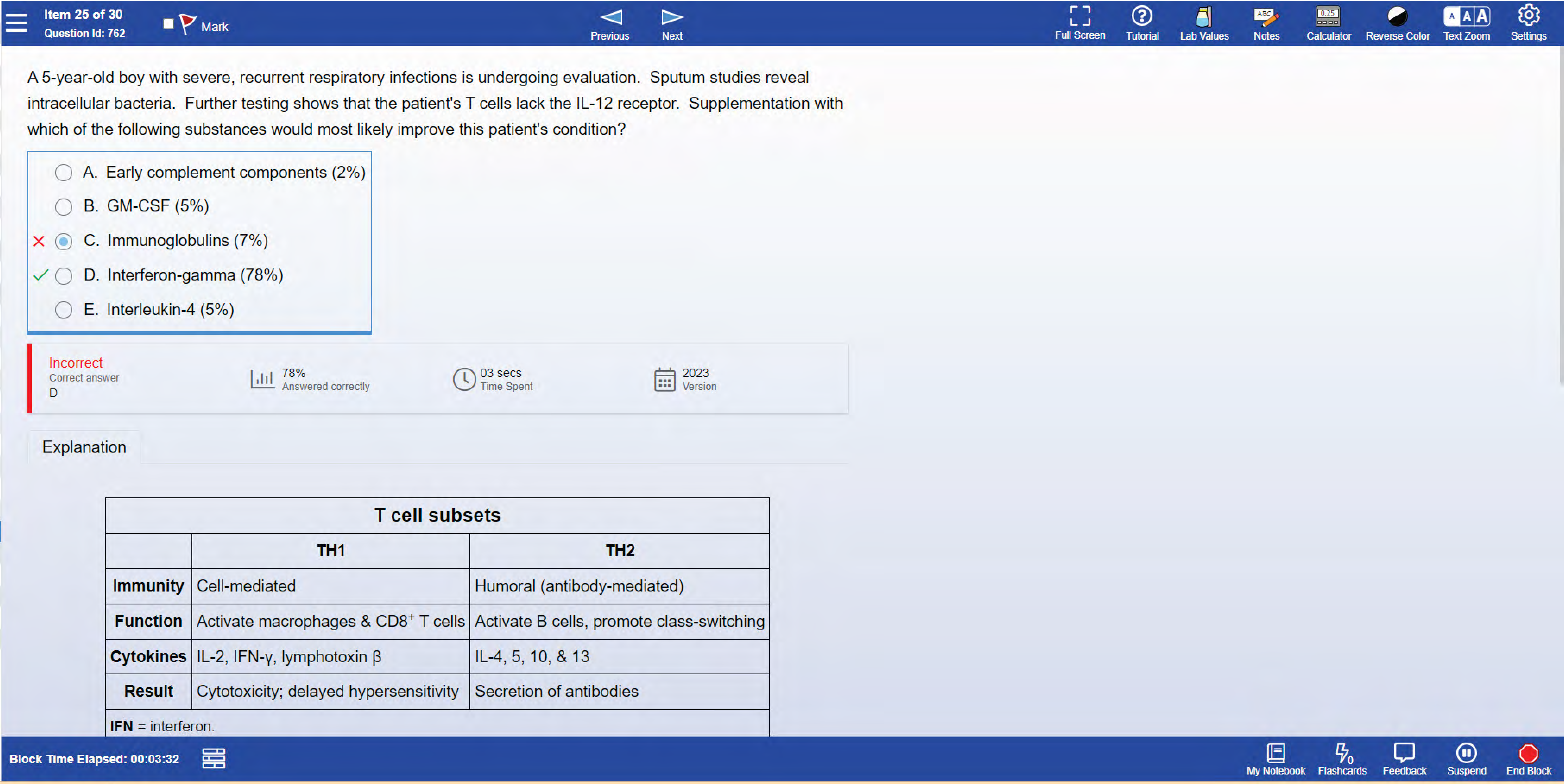
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- ○ A. Early complement components (2%)
- ○ B. GM-CSF (5%)
- ✗ ● C. Immunoglobulins (7%)
- ✓ ○ D. Interferon-gamma (78%)
- ○ E. Interleukin-4 (5%)

Incorrect
Correct answer
D

78%
Answered correctly

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Explanation

T cell subsets		
	TH1	**TH2**
Immunity	Cell-mediated	Humoral (antibody-mediated)
Function	Activate macrophages & $CD8^+$ T cells	Activate B cells, promote class-switching
Cytokines	IL-2, IFN-γ, lymphotoxin β	IL-4, 5, 10, & 13
Result	Cytotoxicity; delayed hypersensitivity	Secretion of antibodies

IFN = interferon.

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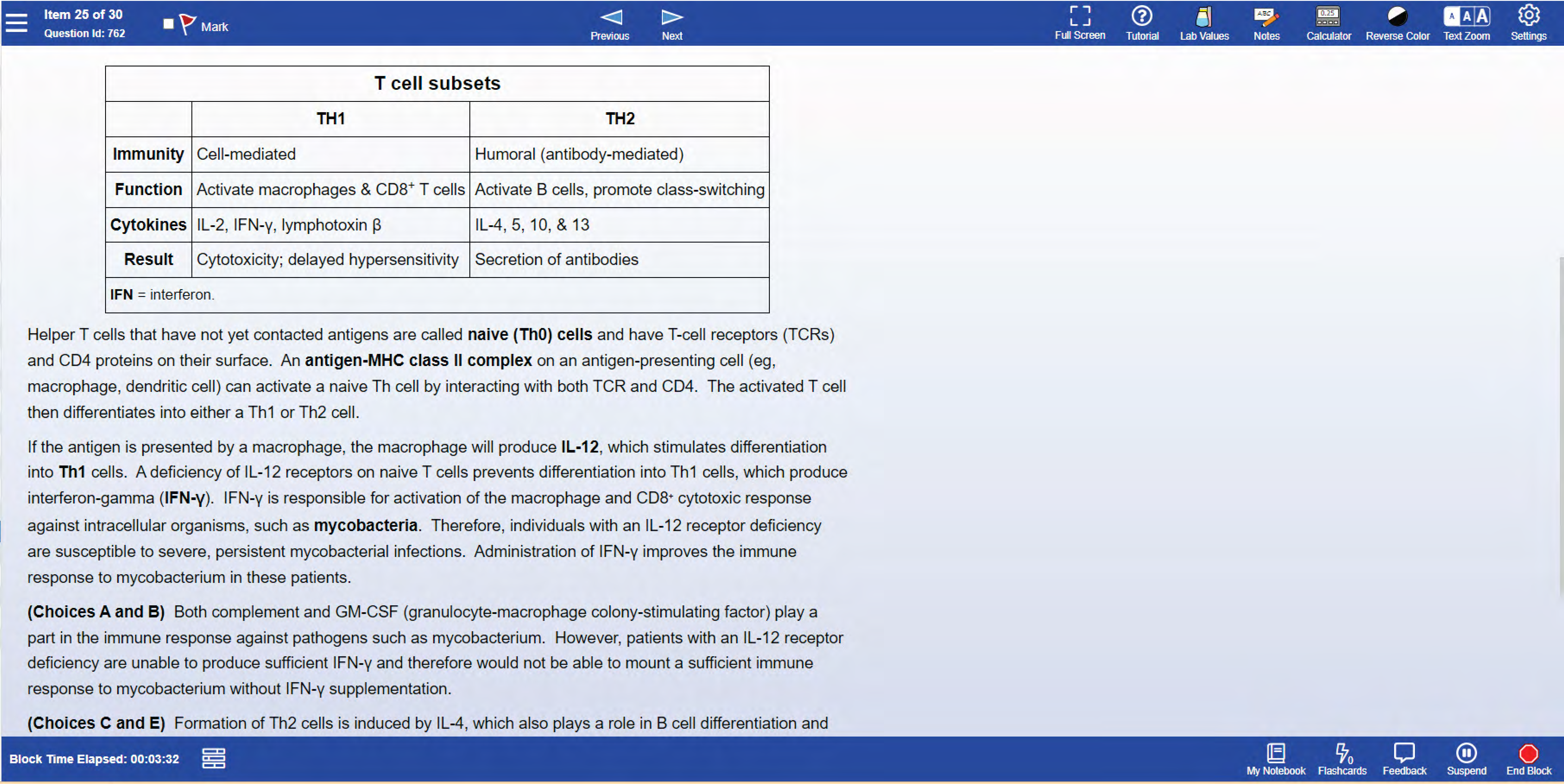
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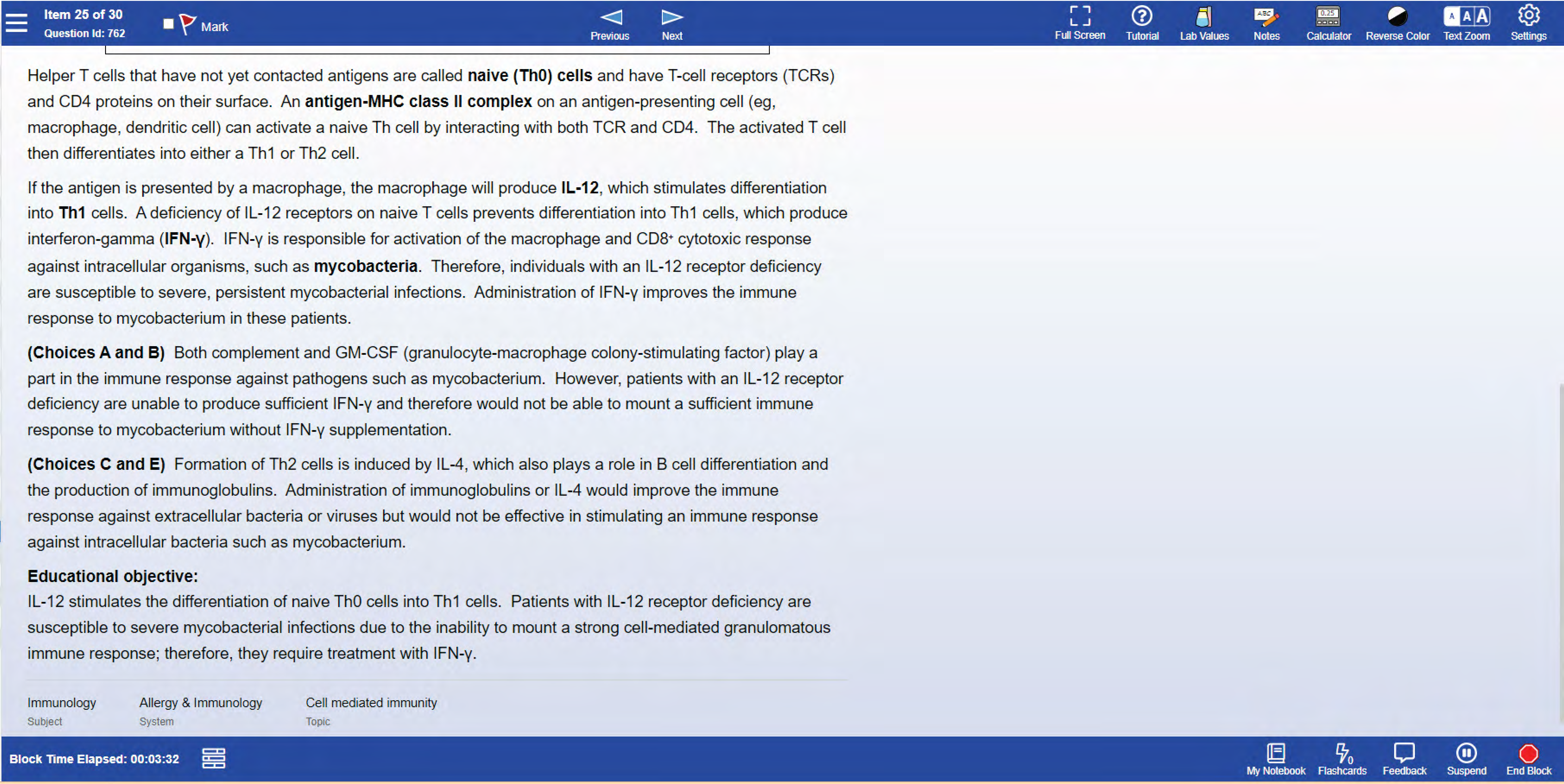
Cytokines	IL-2, IFN-γ, lymphotoxin β	IL-4, 5, 10, & 13
Result	Cytotoxicity; delayed hypersensitivity	Secretion of antibodies
IFN = interferon.		

Helper T cells that have not yet contacted antigens are called **naive (Th0) cells** and have T-cell receptors (TCRs) and CD4 proteins on their surface. An **antigen-MHC class II complex** on an antigen-presenting cell (eg, macrophage, dendritic cell) can activate a naive Th cell by interacting with both TCR and CD4. The activated T cell then differentiates into either a Th1 or Th2 cell.

If the antigen is presented by a macrophage, the macrophage will produce **IL-12**, which stimulates differentiation into **Th1** cells. A deficiency of IL-12 receptors on naive T cells prevents differentiation into Th1 cells, which produce interferon-gamma (**IFN-γ**). IFN-γ is responsible for activation of the macrophage and $CD8^+$ cytotoxic response against intracellular organisms, such as **mycobacteria**. Therefore, individuals with an IL-12 receptor deficiency are susceptible to severe, persistent mycobacterial infections. Administration of IFN-γ improves the immune response to mycobacterium in these patients.

(Choices A and B) Both complement and GM-CSF (granulocyte-macrophage colony-stimulating factor) play a part in the immune response against pathogens such as mycobacterium. However, patients with an IL-12 receptor deficiency are unable to produce sufficient IFN-γ and therefore would not be able to mount a sufficient immune response to mycobacterium without IFN-γ supplementation.

(Choices C and E) Formation of Th2 cells is induced by IL-4, which also plays a role in B cell differentiation and



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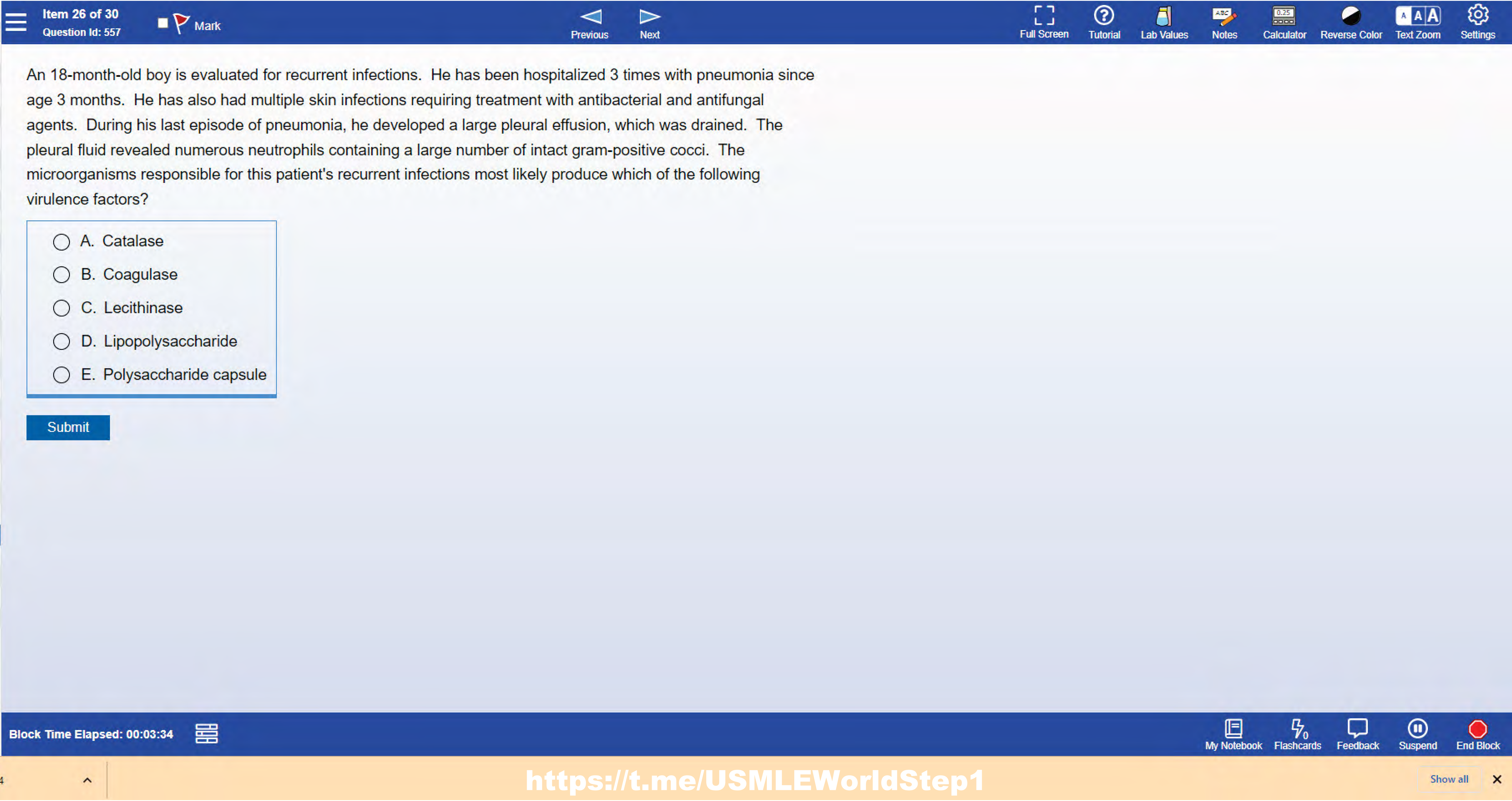
(Choices A and B) Both complement and GM-CSF (granulocyte-macrophage colony-stimulating factor) play a part in the immune response against pathogens such as mycobacterium. However, patients with an IL-12 receptor deficiency are unable to produce sufficient IFN-γ and therefore would not be able to mount a sufficient immune response to mycobacterium without IFN-γ supplementation.

(Choices C and E) Formation of Th2 cells is induced by IL-4, which also plays a role in B cell differentiation and the production of immunoglobulins. Administration of immunoglobulins or IL-4 would improve the immune response against extracellular bacteria or viruses but would not be effective in stimulating an immune response against intracellular bacteria such as mycobacterium.

Educational objective:

IL-12 stimulates the differentiation of naive Th0 cells into Th1 cells. Patients with IL-12 receptor deficiency are susceptible to severe mycobacterial infections due to the inability to mount a strong cell-mediated granulomatous immune response; therefore, they require treatment with IFN-γ.

Immunology	Allergy & Immunology	Cell mediated immunity
Subject	System	Topic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An 18-month-old boy is evaluated for recurrent infections. He has been hospitalized 3 times with pneumonia since age 3 months. He has also had multiple skin infections requiring treatment with antibacterial and antifungal agents. During his last episode of pneumonia, he developed a large pleural effusion, which was drained. The pleural fluid revealed numerous neutrophils containing a large number of intact gram-positive cocci. The microorganisms responsible for this patient's recurrent infections most likely produce which of the following virulence factors?

○ A. Catalase
○ B. Coagulase
○ C. Lecithinase
○ D. Lipopolysaccharide
○ E. Polysaccharide capsule

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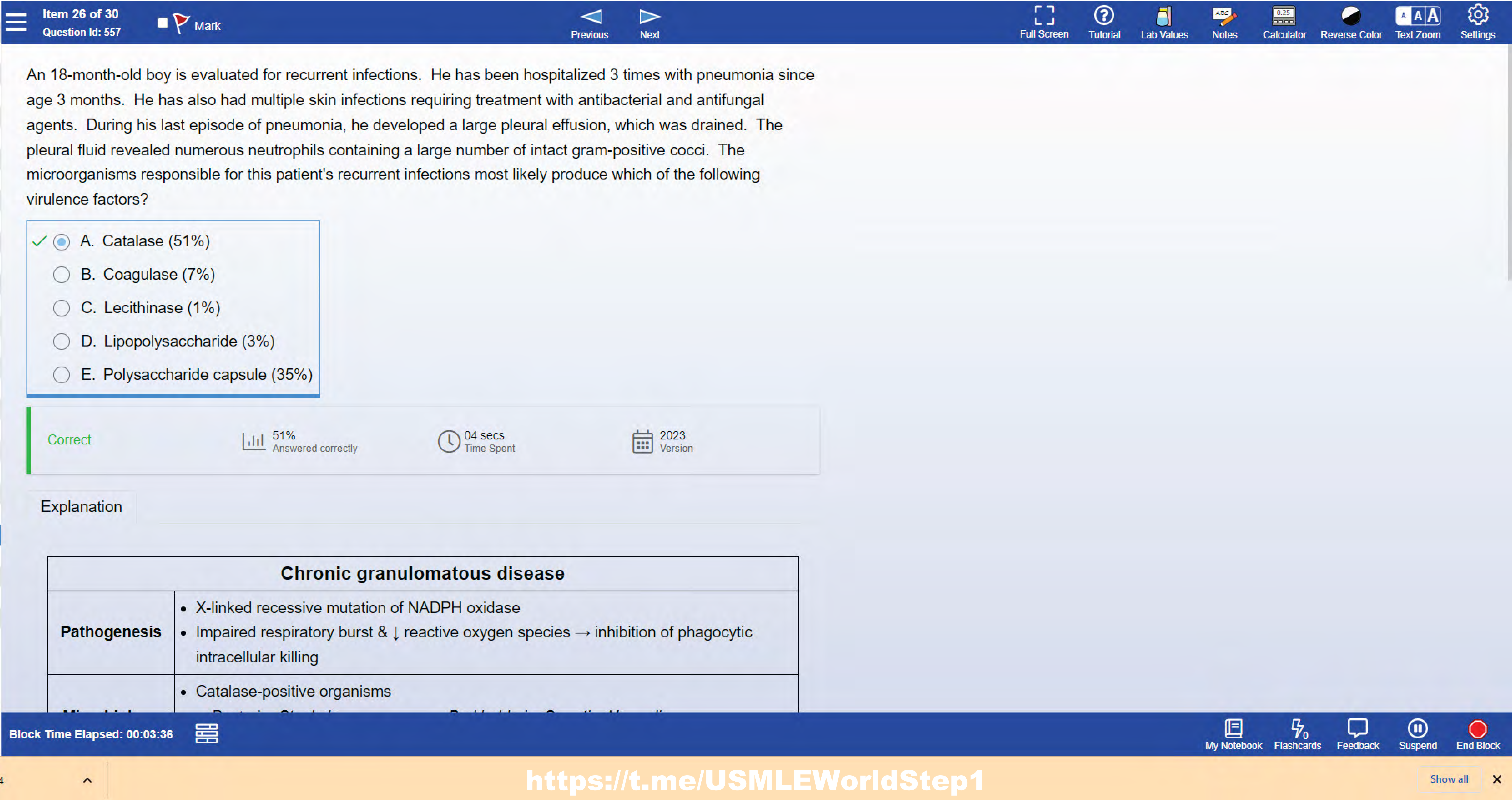
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An 18-month-old boy is evaluated for recurrent infections. He has been hospitalized 3 times with pneumonia since age 3 months. He has also had multiple skin infections requiring treatment with antibacterial and antifungal agents. During his last episode of pneumonia, he developed a large pleural effusion, which was drained. The pleural fluid revealed numerous neutrophils containing a large number of intact gram-positive cocci. The microorganisms responsible for this patient's recurrent infections most likely produce which of the following virulence factors?

✓ ● A. Catalase (51%)
○ B. Coagulase (7%)
○ C. Lecithinase (1%)
○ D. Lipopolysaccharide (3%)
○ E. Polysaccharide capsule (35%)

Correct

51% Answered correctly

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Explanation

Chronic granulomatous disease	
Pathogenesis	• X-linked recessive mutation of NADPH oxidase • Impaired respiratory burst & ↓ reactive oxygen species → inhibition of phagocytic intracellular killing
	• Catalase-positive organisms

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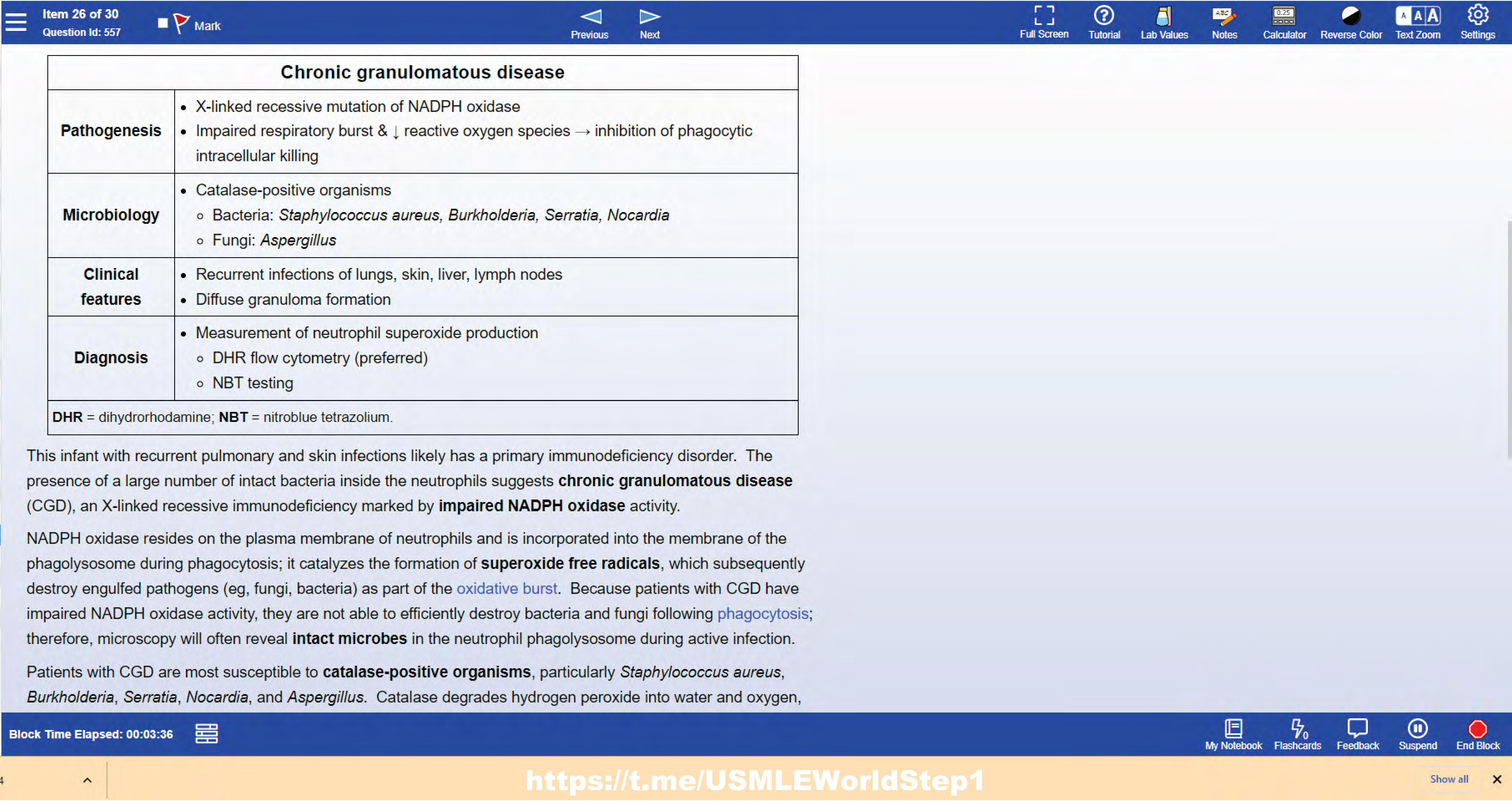
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Chronic granulomatous disease

Pathogenesis	• X-linked recessive mutation of NADPH oxidase • Impaired respiratory burst & ↓ reactive oxygen species → inhibition of phagocytic intracellular killing
Microbiology	• Catalase-positive organisms ◦ Bacteria: *Staphylococcus aureus, Burkholderia, Serratia, Nocardia* ◦ Fungi: *Aspergillus*
Clinical features	• Recurrent infections of lungs, skin, liver, lymph nodes • Diffuse granuloma formation
Diagnosis	• Measurement of neutrophil superoxide production ◦ DHR flow cytometry (preferred) ◦ NBT testing

DHR = dihydrorhodamine; **NBT** = nitroblue tetrazolium.

This infant with recurrent pulmonary and skin infections likely has a primary immunodeficiency disorder. The presence of a large number of intact bacteria inside the neutrophils suggests **chronic granulomatous disease** (CGD), an X-linked recessive immunodeficiency marked by **impaired NADPH oxidase** activity.

NADPH oxidase resides on the plasma membrane of neutrophils and is incorporated into the membrane of the phagolysosome during phagocytosis; it catalyzes the formation of **superoxide free radicals**, which subsequently destroy engulfed pathogens (eg, fungi, bacteria) as part of the oxidative burst. Because patients with CGD have impaired NADPH oxidase activity, they are not able to efficiently destroy bacteria and fungi following phagocytosis; therefore, microscopy will often reveal **intact microbes** in the neutrophil phagolysosome during active infection.

Patients with CGD are most susceptible to **catalase-positive organisms**, particularly *Staphylococcus aureus*, *Burkholderia*, *Serratia*, *Nocardia*, and *Aspergillus*. Catalase degrades hydrogen peroxide into water and oxygen,

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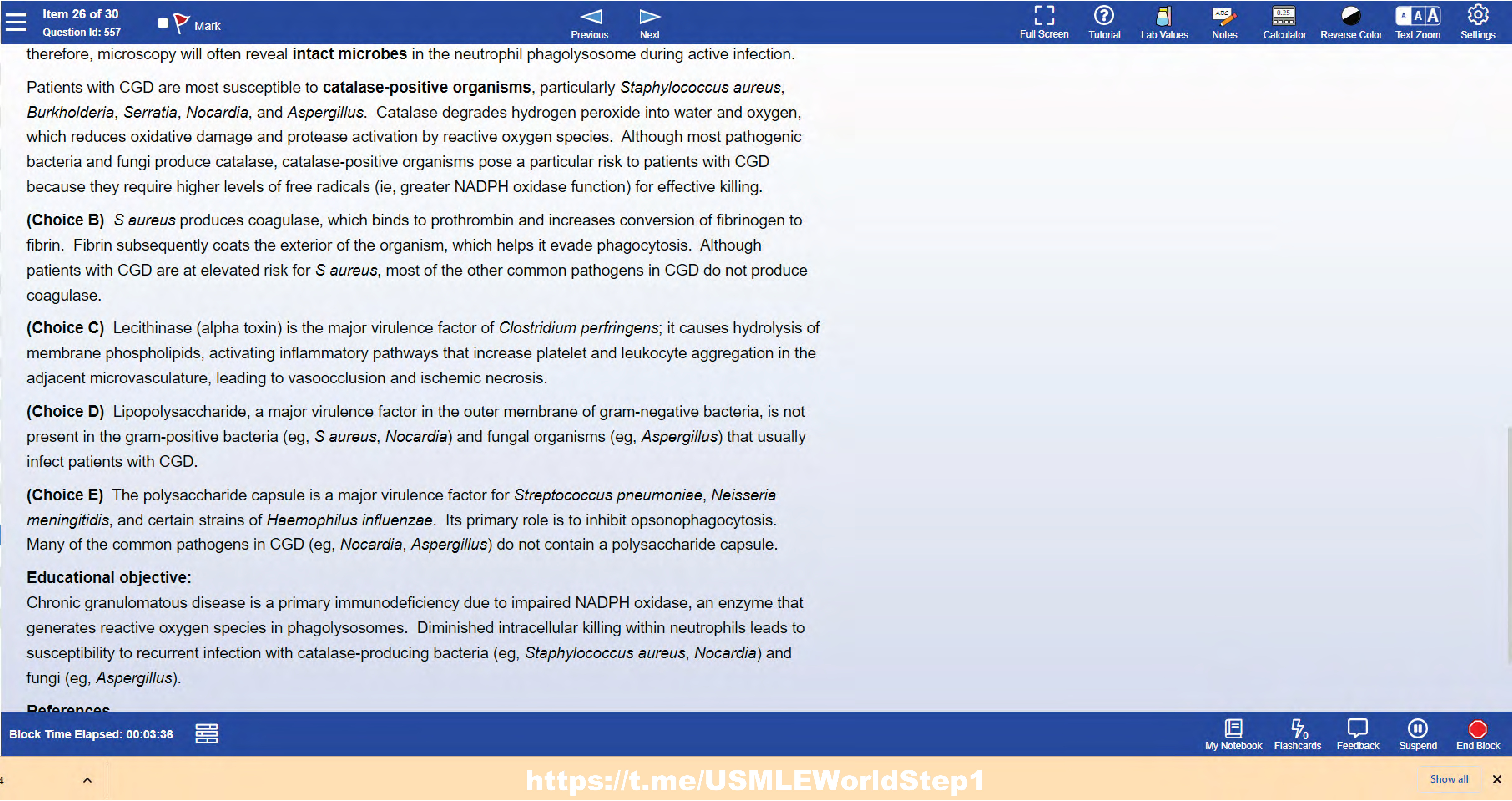


therefore, microscopy will often reveal **intact microbes** in the neutrophil phagolysosome during active infection.

Patients with CGD are most susceptible to **catalase-positive organisms**, particularly *Staphylococcus aureus*, *Burkholderia*, *Serratia*, *Nocardia*, and *Aspergillus*. Catalase degrades hydrogen peroxide into water and oxygen, which reduces oxidative damage and protease activation by reactive oxygen species. Although most pathogenic bacteria and fungi produce catalase, catalase-positive organisms pose a particular risk to patients with CGD because they require higher levels of free radicals (ie, greater NADPH oxidase function) for effective killing.

(Choice B) *S aureus* produces coagulase, which binds to prothrombin and increases conversion of fibrinogen to fibrin. Fibrin subsequently coats the exterior of the organism, which helps it evade phagocytosis. Although patients with CGD are at elevated risk for *S aureus*, most of the other common pathogens in CGD do not produce coagulase.

(Choice C) Lecithinase (alpha toxin) is the major virulence factor of *Clostridium perfringens*; it causes hydrolysis of membrane phospholipids, activating inflammatory pathways that increase platelet and leukocyte aggregation in the adjacent microvasculature, leading to vasoocclusion and ischemic necrosis.

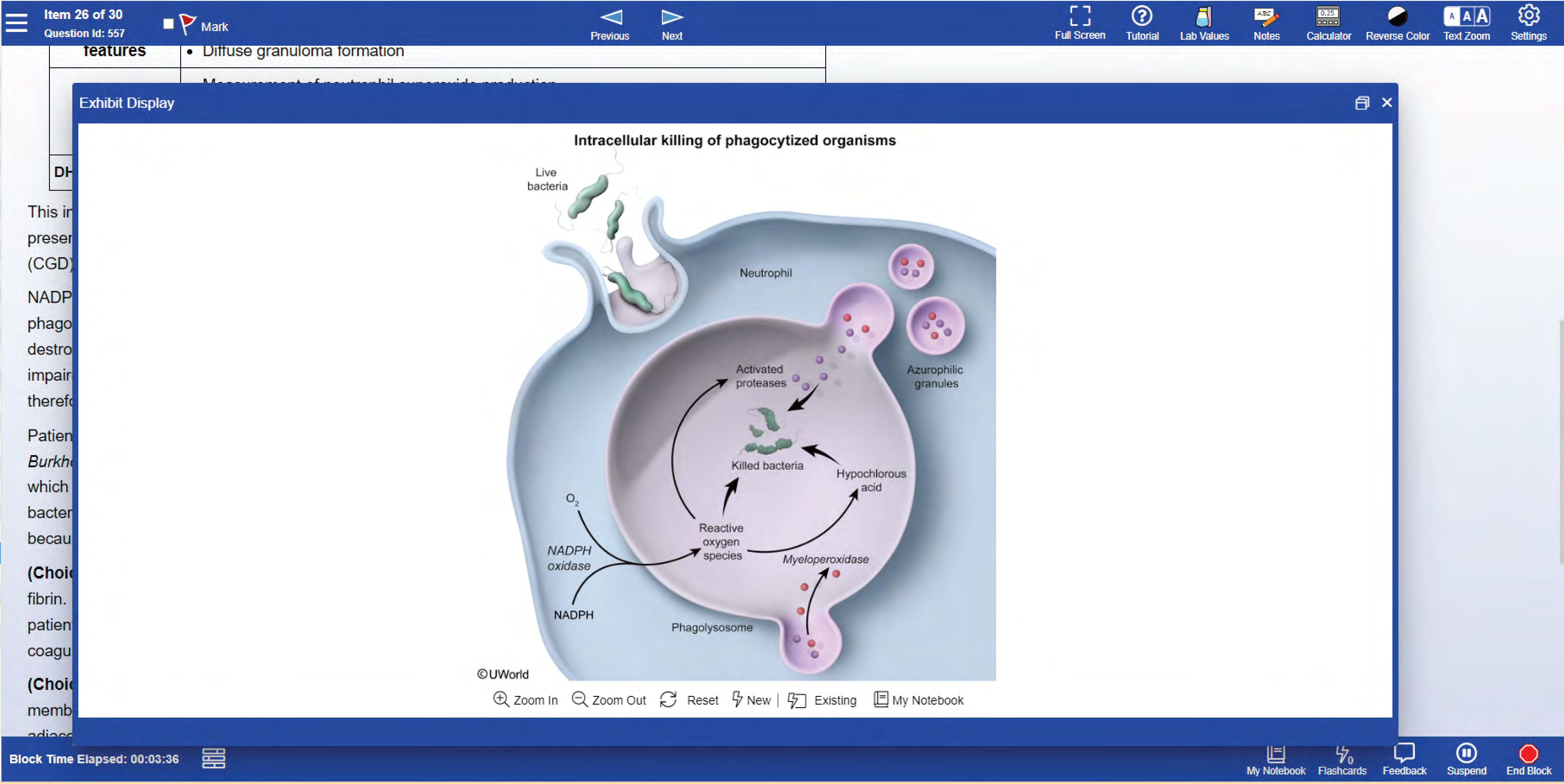
(Choice D) Lipopolysaccharide, a major virulence factor in the outer membrane of gram-negative bacteria, is not present in the gram-positive bacteria (eg, *S aureus*, *Nocardia*) and fungal organisms (eg, *Aspergillus*) that usually infect patients with CGD.

(Choice E) The polysaccharide capsule is a major virulence factor for *Streptococcus pneumoniae*, *Neisseria meningitidis*, and certain strains of *Haemophilus influenzae*. Its primary role is to inhibit opsonophagocytosis. Many of the common pathogens in CGD (eg, *Nocardia*, *Aspergillus*) do not contain a polysaccharide capsule.

Educational objective:

Chronic granulomatous disease is a primary immunodeficiency due to impaired NADPH oxidase, an enzyme that generates reactive oxygen species in phagolysosomes. Diminished intracellular killing within neutrophils leads to susceptibility to recurrent infection with catalase-producing bacteria (eg, *Staphylococcus aureus*, *Nocardia*) and fungi (eg, *Aspergillus*).

References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Intracellular killing of phagocytized organisms
Live bacteria
Neutrophil
Azurophilic granules
Activated proteases
Killed bacteria
Hypochlorous acid
O_2
Reactive oxygen species
NADPH oxidase
NADPH
Myeloperoxidase
Phagolysosome
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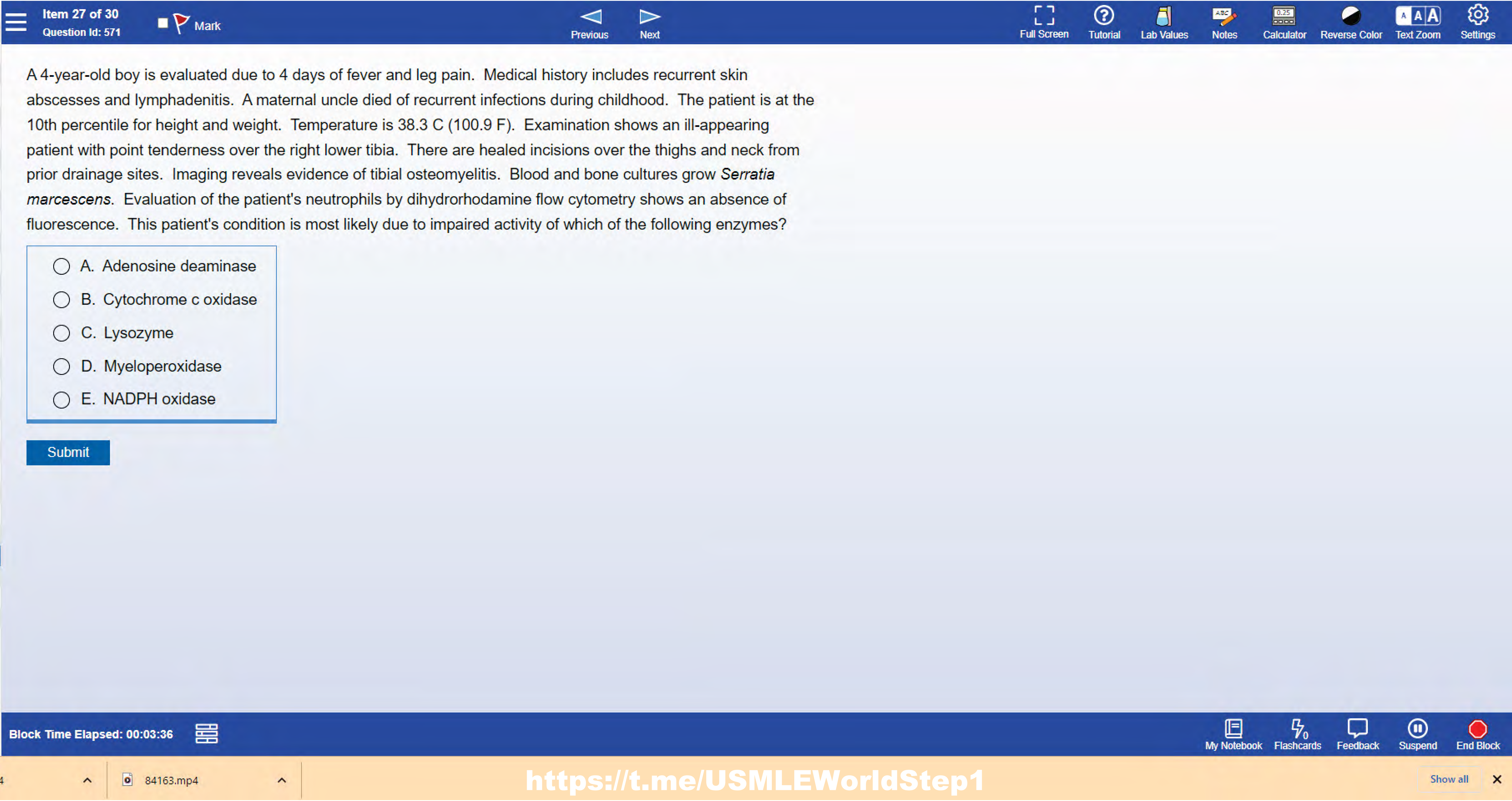
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A 4-year-old boy is evaluated due to 4 days of fever and leg pain. Medical history includes recurrent skin abscesses and lymphadenitis. A maternal uncle died of recurrent infections during childhood. The patient is at the 10th percentile for height and weight. Temperature is 38.3 C (100.9 F). Examination shows an ill-appearing patient with point tenderness over the right lower tibia. There are healed incisions over the thighs and neck from prior drainage sites. Imaging reveals evidence of tibial osteomyelitis. Blood and bone cultures grow *Serratia marcescens*. Evaluation of the patient's neutrophils by dihydrorhodamine flow cytometry shows an absence of fluorescence. This patient's condition is most likely due to impaired activity of which of the following enzymes?

○ A. Adenosine deaminase
○ B. Cytochrome c oxidase
○ C. Lysozyme
○ D. Myeloperoxidase
○ E. NADPH oxidase

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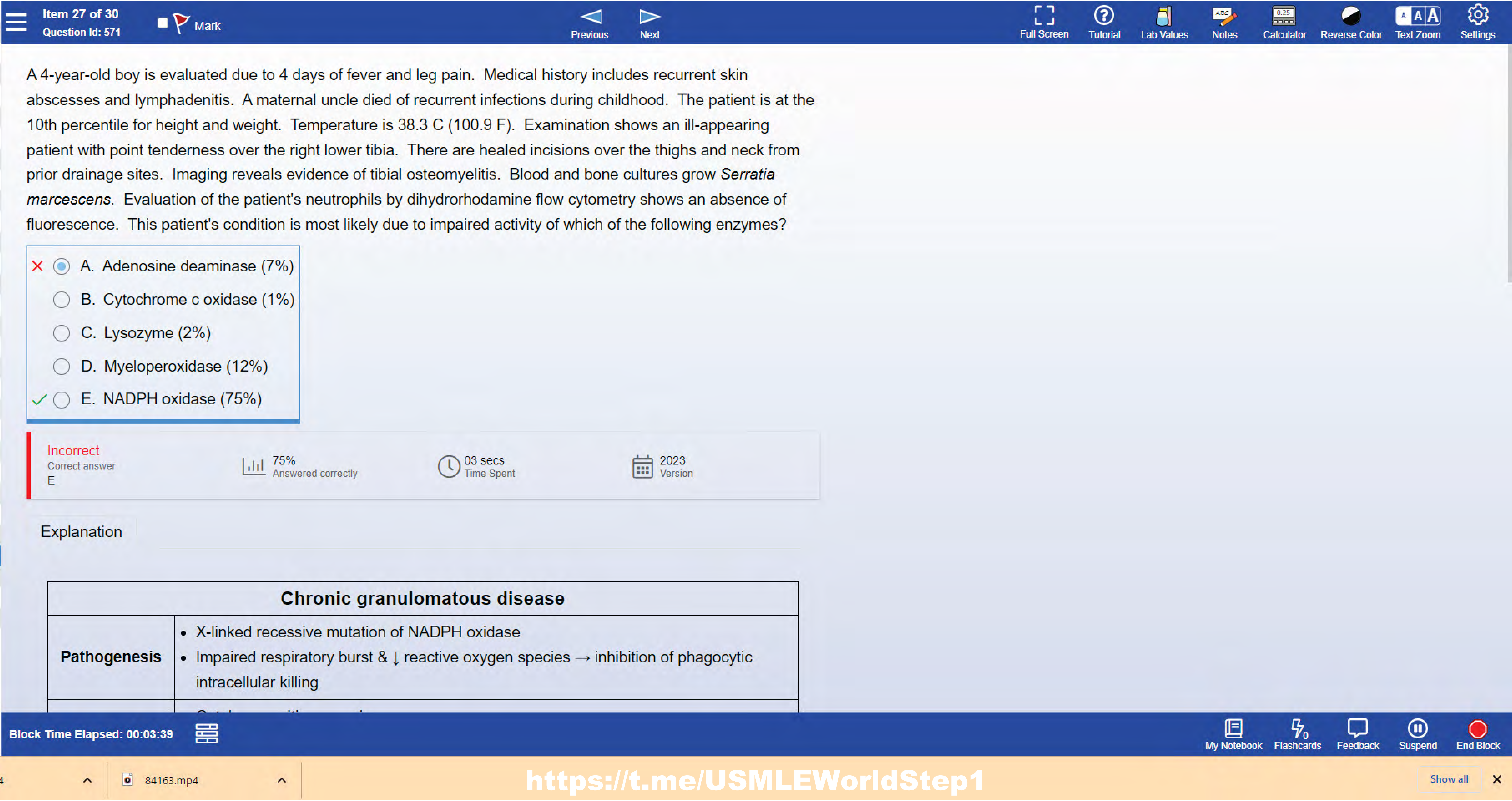
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- ✗ ● A. Adenosine deaminase (7%)
- ○ B. Cytochrome c oxidase (1%)
- ○ C. Lysozyme (2%)
- ○ D. Myeloperoxidase (12%)
- ✓ ○ E. NADPH oxidase (75%)

Incorrect
Correct answer
E

75%
Answered correctly

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2023
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Explanation

Chronic granulomatous disease	
Pathogenesis	• X-linked recessive mutation of NADPH oxidase • Impaired respiratory burst & ↓ reactive oxygen species → inhibition of phagocytic intracellular killing

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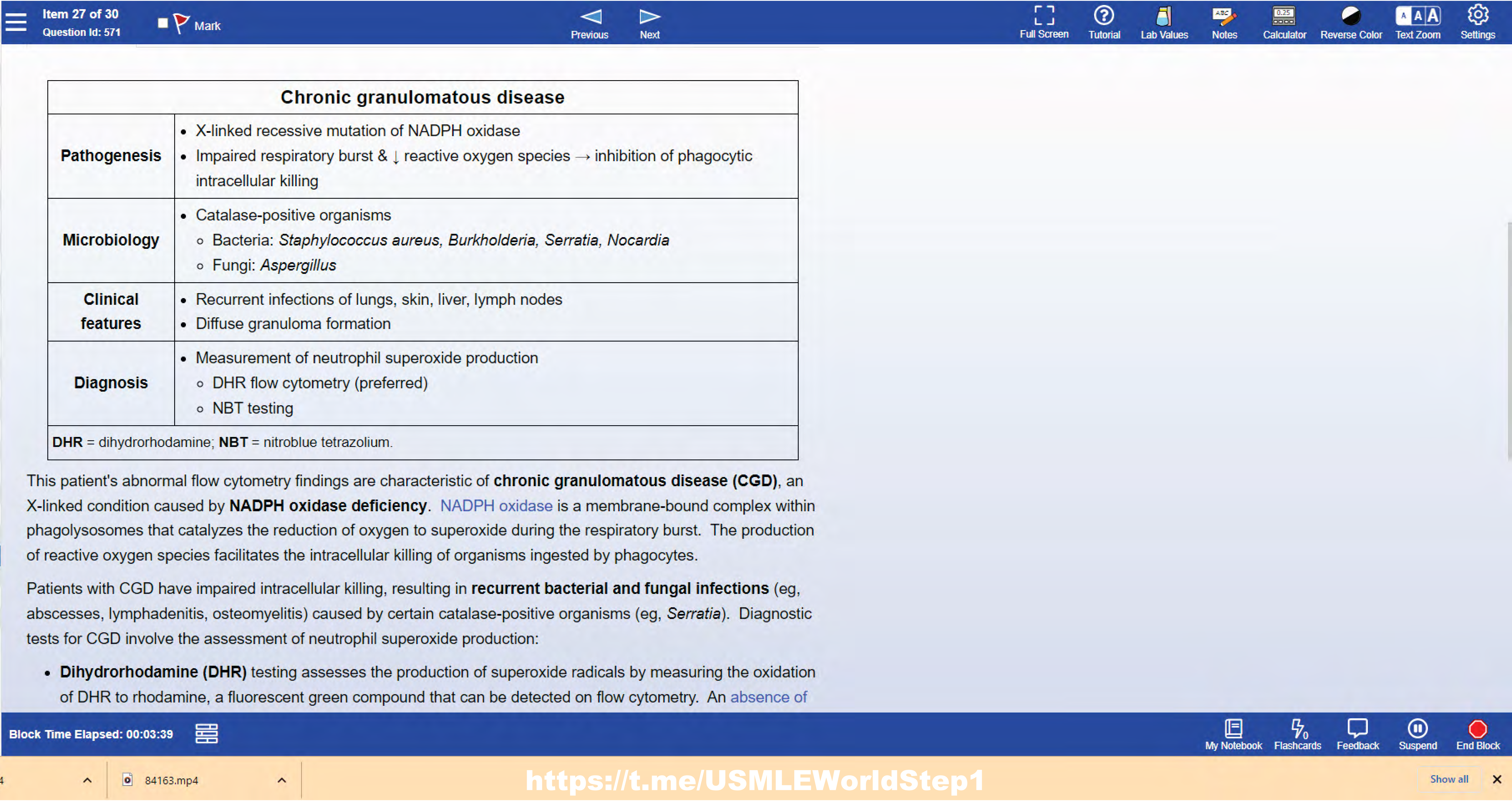
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Clinical features	• Recurrent infections of lungs, skin, liver, lymph nodes • Diffuse granuloma formation
Diagnosis	• Measurement of neutrophil superoxide production ○ DHR flow cytometry (preferred) ○ NBT testing
DHR = dihydrorhodamine; **NBT** = nitroblue tetrazolium.	

This patient's abnormal flow cytometry findings are characteristic of **chronic granulomatous disease (CGD)**, an X-linked condition caused by **NADPH oxidase deficiency**. NADPH oxidase is a membrane-bound complex within phagolysosomes that catalyzes the reduction of oxygen to superoxide during the respiratory burst. The production of reactive oxygen species facilitates the intracellular killing of organisms ingested by phagocytes.

Patients with CGD have impaired intracellular killing, resulting in **recurrent bacterial and fungal infections** (eg, abscesses, lymphadenitis, osteomyelitis) caused by certain catalase-positive organisms (eg, *Serratia*). Diagnostic tests for CGD involve the assessment of neutrophil superoxide production:

- **Dihydrorhodamine (DHR)** testing assesses the production of superoxide radicals by measuring the oxidation of DHR to rhodamine, a fluorescent green compound that can be detected on flow cytometry. An absence of

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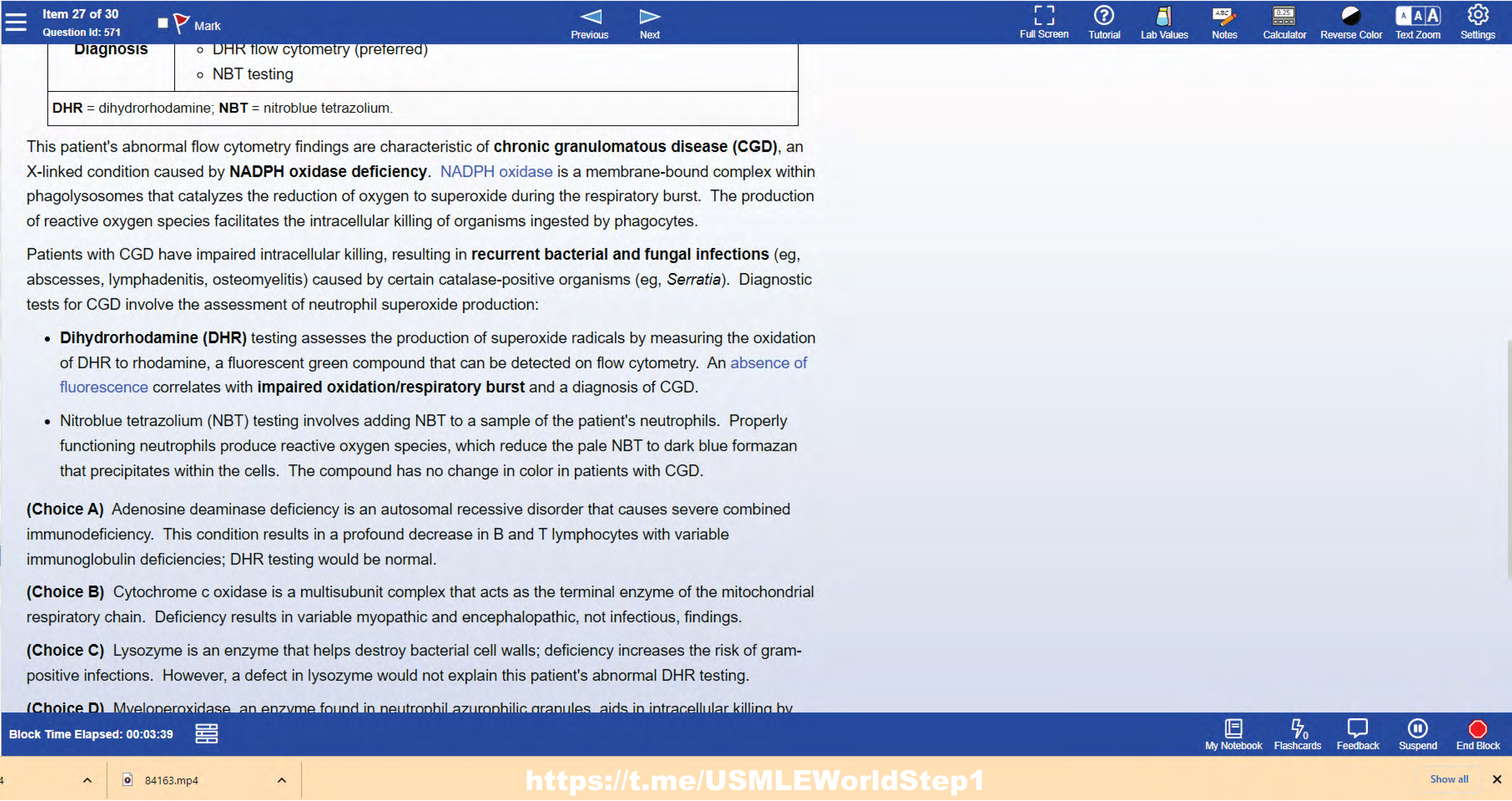

Diagnosis	◦ DHR flow cytometry (preferred) ◦ NBT testing
DHR = dihydrorhodamine; **NBT** = nitroblue tetrazolium.	

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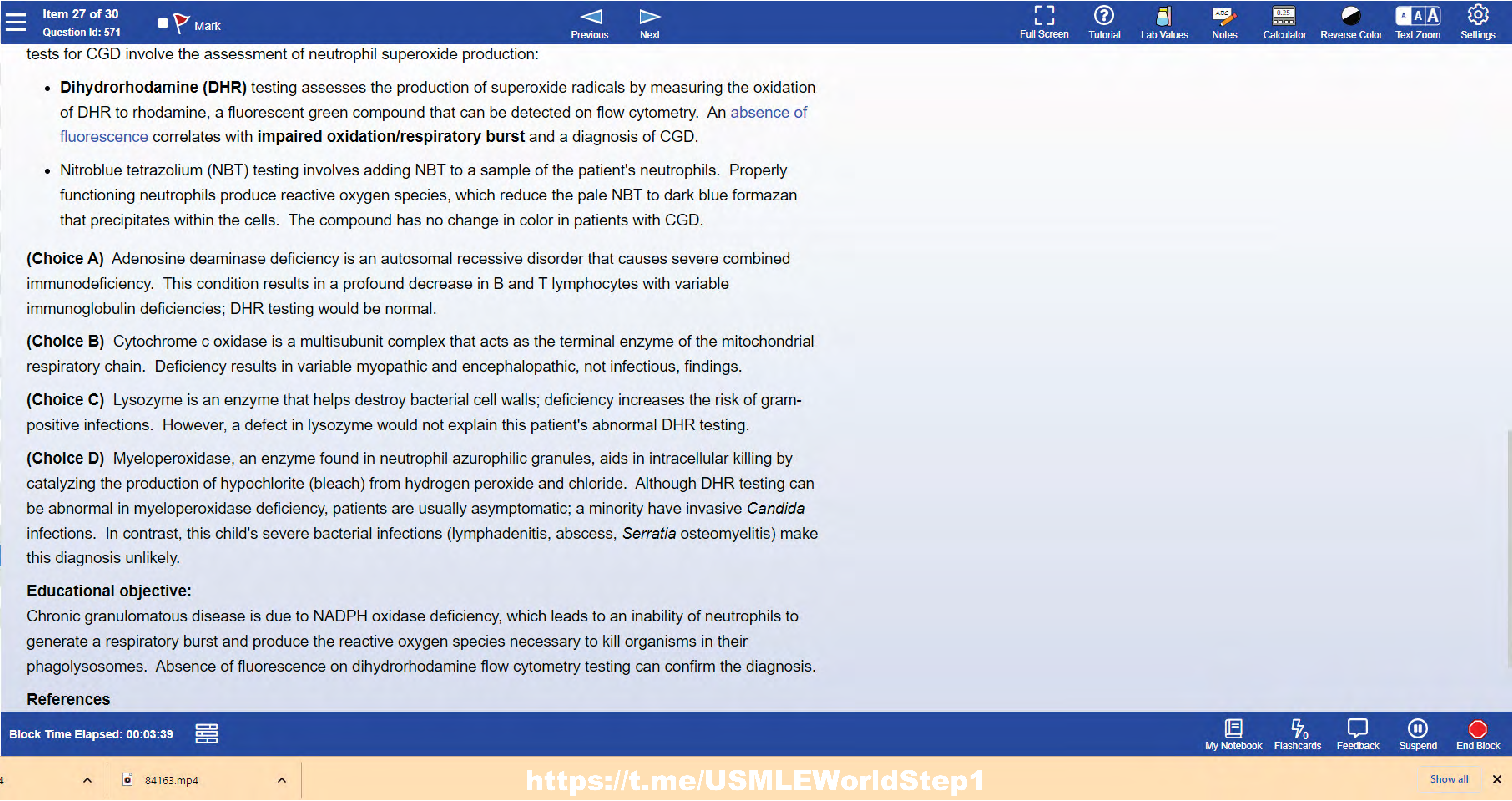
- **Dihydrorhodamine (DHR)** testing assesses the production of superoxide radicals by measuring the oxidation of DHR to rhodamine, a fluorescent green compound that can be detected on flow cytometry. An absence of fluorescence correlates with **impaired oxidation/respiratory burst** and a diagnosis of CGD.
- Nitroblue tetrazolium (NBT) testing involves adding NBT to a sample of the patient's neutrophils. Properly functioning neutrophils produce reactive oxygen species, which reduce the pale NBT to dark blue formazan that precipitates within the cells. The compound has no change in color in patients with CGD.

(Choice A) Adenosine deaminase deficiency is an autosomal recessive disorder that causes severe combined immunodeficiency. This condition results in a profound decrease in B and T lymphocytes with variable immunoglobulin deficiencies; DHR testing would be normal.

(Choice B) Cytochrome c oxidase is a multisubunit complex that acts as the terminal enzyme of the mitochondrial respiratory chain. Deficiency results in variable myopathic and encephalopathic, not infectious, findings.

(Choice C) Lysozyme is an enzyme that helps destroy bacterial cell walls; deficiency increases the risk of gram-positive infections. However, a defect in lysozyme would not explain this patient's abnormal DHR testing.

(Choice D) Myeloperoxidase, an enzyme found in neutrophil azurophilic granules, aids in intracellular killing by



tests for CGD involve the assessment of neutrophil superoxide production:

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(Choice B) Cytochrome c oxidase is a multisubunit complex that acts as the terminal enzyme of the mitochondrial respiratory chain. Deficiency results in variable myopathic and encephalopathic, not infectious, findings.

(Choice C) Lysozyme is an enzyme that helps destroy bacterial cell walls; deficiency increases the risk of gram-positive infections. However, a defect in lysozyme would not explain this patient's abnormal DHR testing.

(Choice D) Myeloperoxidase, an enzyme found in neutrophil azurophilic granules, aids in intracellular killing by catalyzing the production of hypochlorite (bleach) from hydrogen peroxide and chloride. Although DHR testing can be abnormal in myeloperoxidase deficiency, patients are usually asymptomatic; a minority have invasive *Candida* infections. In contrast, this child's severe bacterial infections (lymphadenitis, abscess, *Serratia* osteomyelitis) make this diagnosis unlikely.

Educational objective:

Chronic granulomatous disease is due to NADPH oxidase deficiency, which leads to an inability of neutrophils to generate a respiratory burst and produce the reactive oxygen species necessary to kill organisms in their phagolysosomes. Absence of fluorescence on dihydrorhodamine flow cytometry testing can confirm the diagnosis.

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Diagnosis

- DHR flow cytometry (preferred)
- NBT testing

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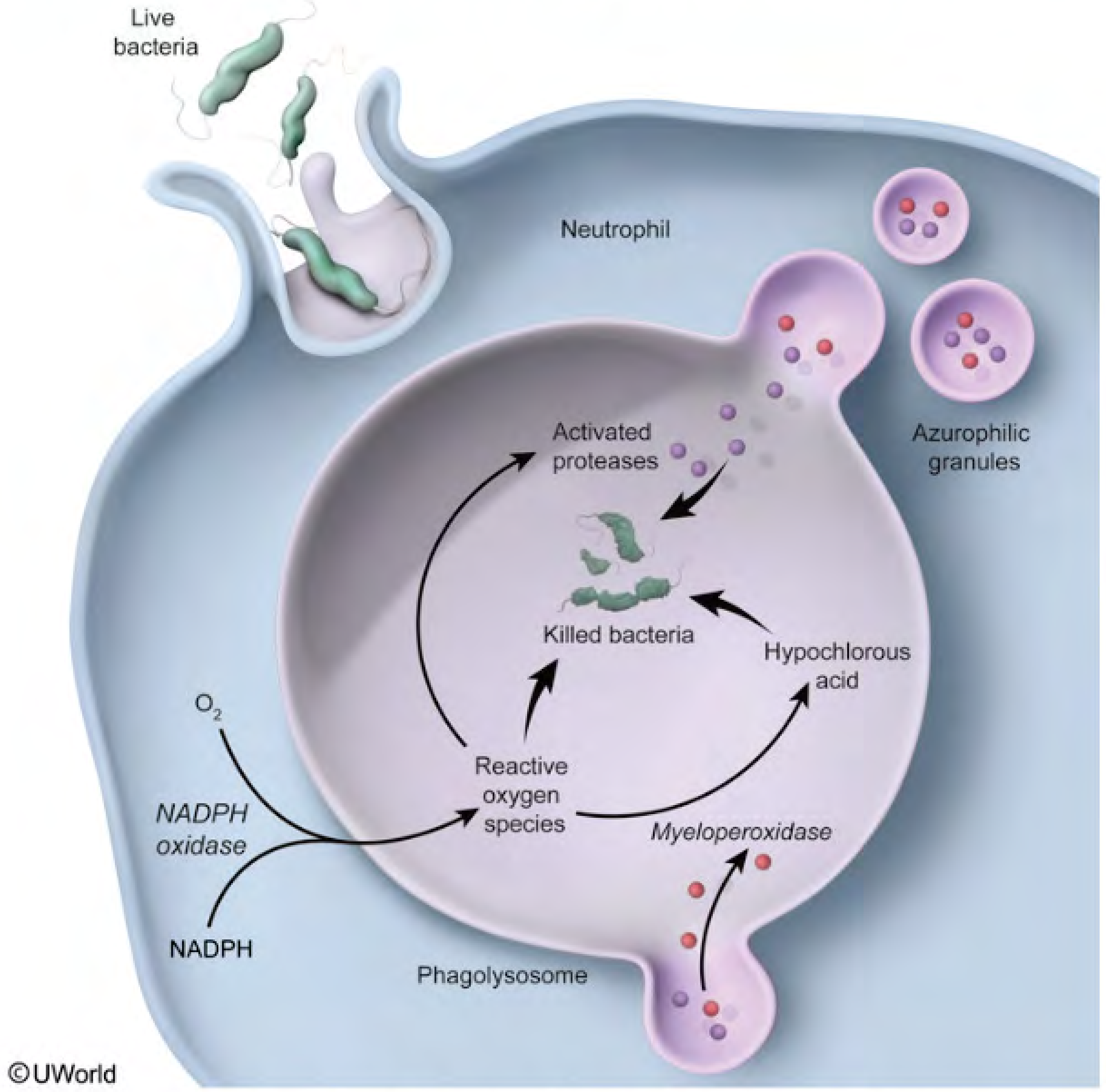
Live bacteria
Neutrophil
Azurophilic granules
Activated proteases
Killed bacteria
Hypochlorous acid
O_2
Reactive oxygen species
NADPH oxidase
Myeloperoxidase
NADPH
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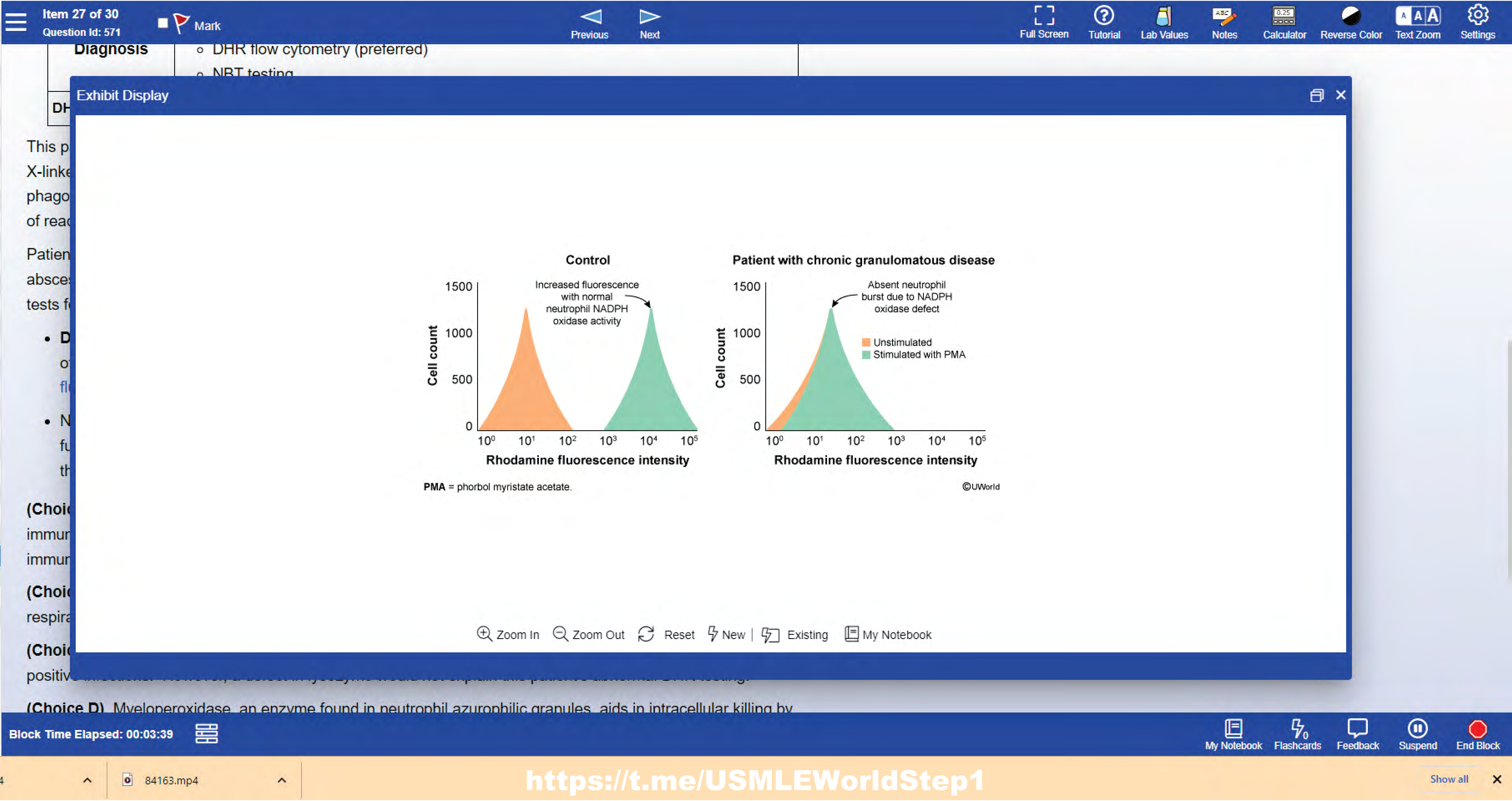
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(Choice D) Myeloperoxidase, an enzyme found in neutrophil azurophilic granules, aids in intracellular killing by

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Increased fluorescence with normal neutrophil NADPH oxidase activity
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10^3
10^4
10^5
Rhodamine fluorescence intensity
Patient with chronic granulomatous disease
Absent neutrophil burst due to NADPH oxidase defect
🟧 Unstimulated
🟩 Stimulated with PMA
Cell count
1500
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500
0
10^0
10^1
10^2
10^3
10^4
10^5
Rhodamine fluorescence intensity

PMA = phorbol myristate acetate.

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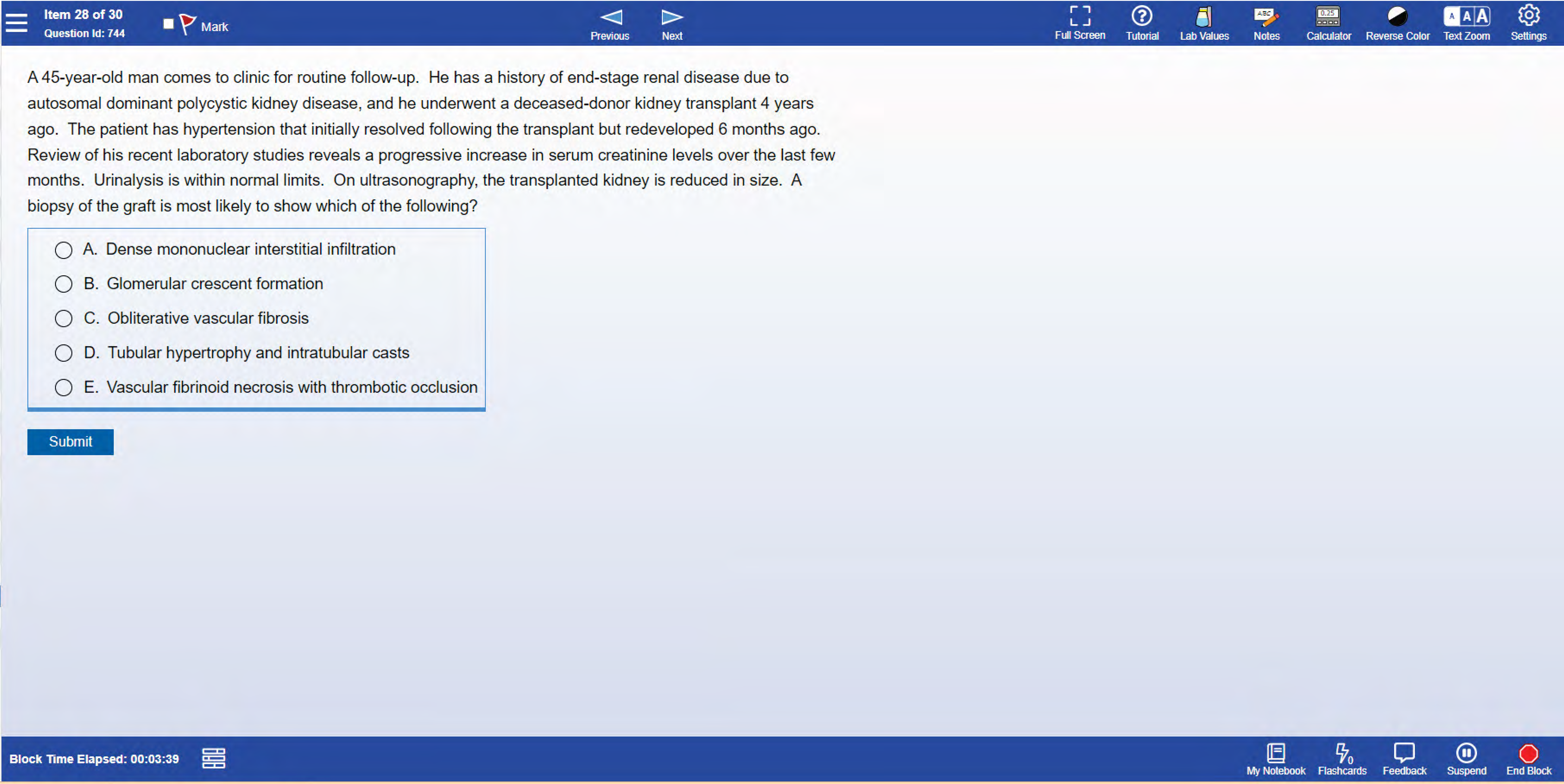
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A 45-year-old man comes to clinic for routine follow-up. He has a history of end-stage renal disease due to autosomal dominant polycystic kidney disease, and he underwent a deceased-donor kidney transplant 4 years ago. The patient has hypertension that initially resolved following the transplant but redeveloped 6 months ago. Review of his recent laboratory studies reveals a progressive increase in serum creatinine levels over the last few months. Urinalysis is within normal limits. On ultrasonography, the transplanted kidney is reduced in size. A biopsy of the graft is most likely to show which of the following?

- ○ A. Dense mononuclear interstitial infiltration
- ○ B. Glomerular crescent formation
- ○ C. Obliterative vascular fibrosis
- ○ D. Tubular hypertrophy and intratubular casts
- ○ E. Vascular fibrinoid necrosis with thrombotic occlusion

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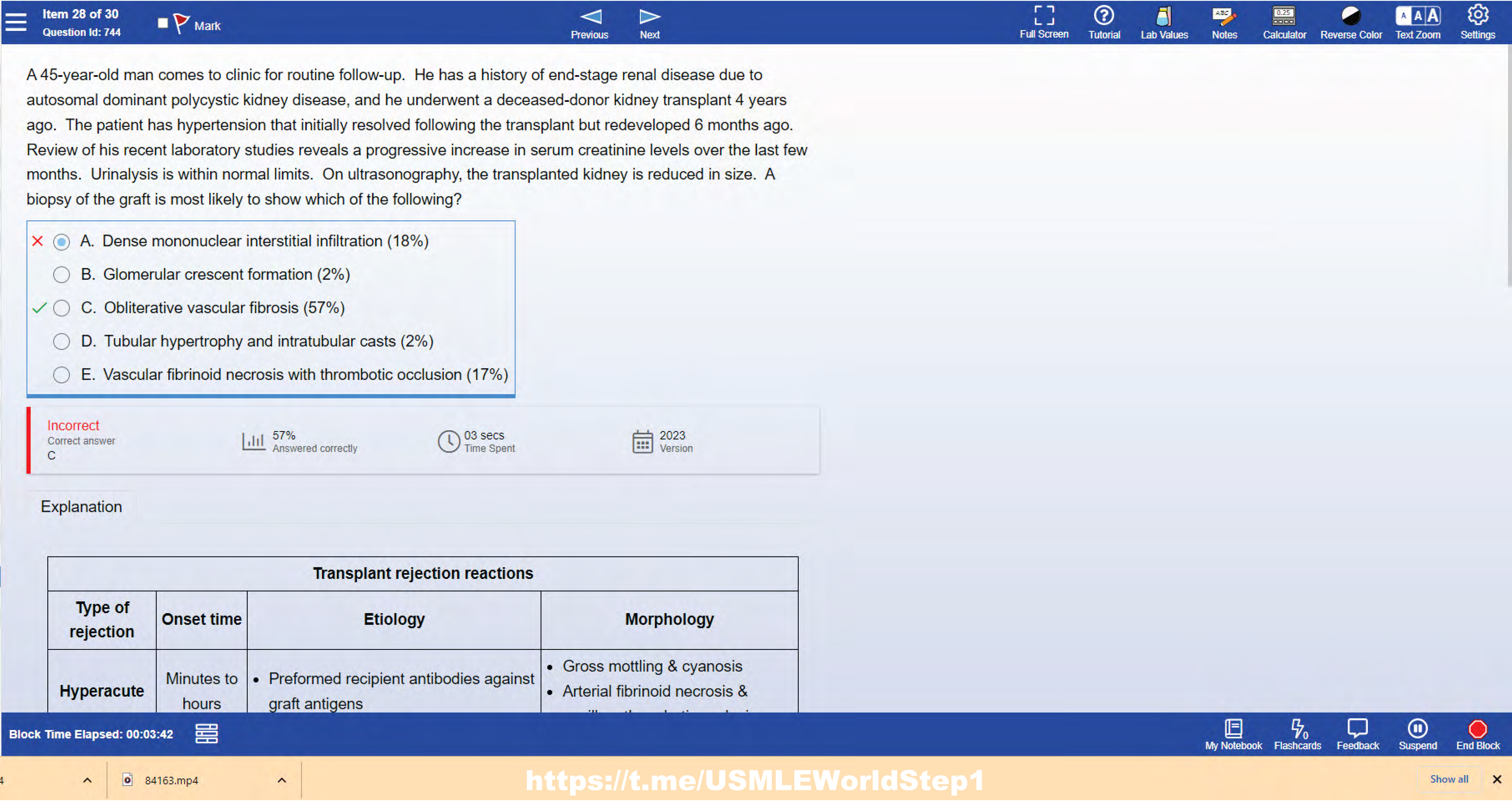
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- ✗ ● A. Dense mononuclear interstitial infiltration (18%)
- ○ B. Glomerular crescent formation (2%)
- ✓ ○ C. Obliterative vascular fibrosis (57%)
- ○ D. Tubular hypertrophy and intratubular casts (2%)
- ○ E. Vascular fibrinoid necrosis with thrombotic occlusion (17%)

Incorrect
Correct answer
C

57%
Answered correctly

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Explanation

Transplant rejection reactions			
Type of rejection	**Onset time**	**Etiology**	**Morphology**
Hyperacute	Minutes to hours	• Preformed recipient antibodies against graft antigens	• Gross mottling & cyanosis • Arterial fibrinoid necrosis &

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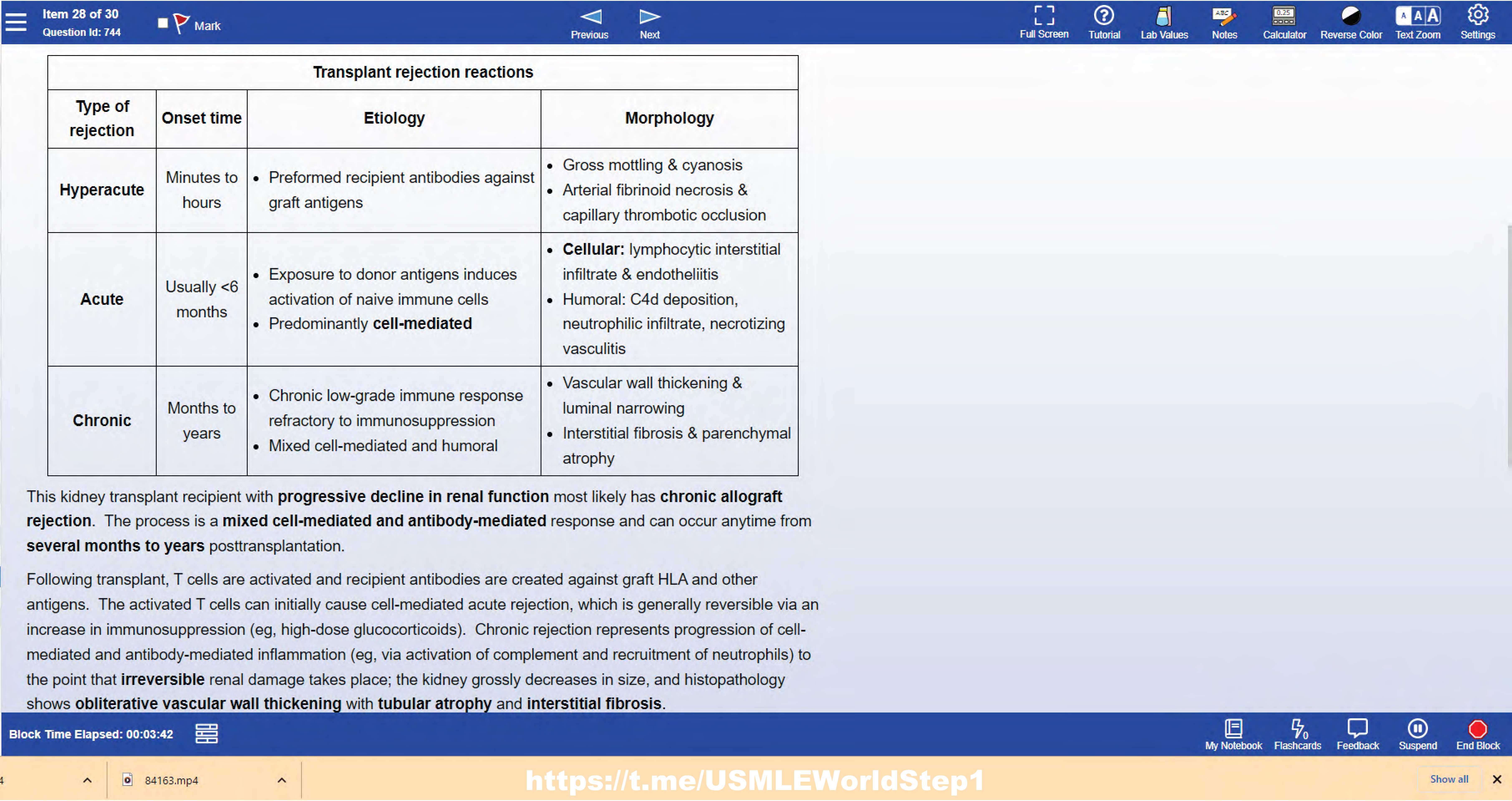
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Transplant rejection reactions			
Type of rejection	**Onset time**	**Etiology**	**Morphology**
Hyperacute	Minutes to hours	• Preformed recipient antibodies against graft antigens	• Gross mottling & cyanosis • Arterial fibrinoid necrosis & capillary thrombotic occlusion
Acute	Usually <6 months	• Exposure to donor antigens induces activation of naive immune cells • Predominantly **cell-mediated**	• **Cellular:** lymphocytic interstitial infiltrate & endotheliitis • Humoral: C4d deposition, neutrophilic infiltrate, necrotizing vasculitis
Chronic	Months to years	• Chronic low-grade immune response refractory to immunosuppression • Mixed cell-mediated and humoral	• Vascular wall thickening & luminal narrowing • Interstitial fibrosis & parenchymal atrophy

This kidney transplant recipient with **progressive decline in renal function** most likely has **chronic allograft rejection**. The process is a **mixed cell-mediated and antibody-mediated** response and can occur anytime from **several months to years** posttransplantation.

Following transplant, T cells are activated and recipient antibodies are created against graft HLA and other antigens. The activated T cells can initially cause cell-mediated acute rejection, which is generally reversible via an increase in immunosuppression (eg, high-dose glucocorticoids). Chronic rejection represents progression of cell-mediated and antibody-mediated inflammation (eg, via activation of complement and recruitment of neutrophils) to the point that **irreversible** renal damage takes place; the kidney grossly decreases in size, and histopathology shows **obliterative vascular wall thickening** with **tubular atrophy** and **interstitial fibrosis**.

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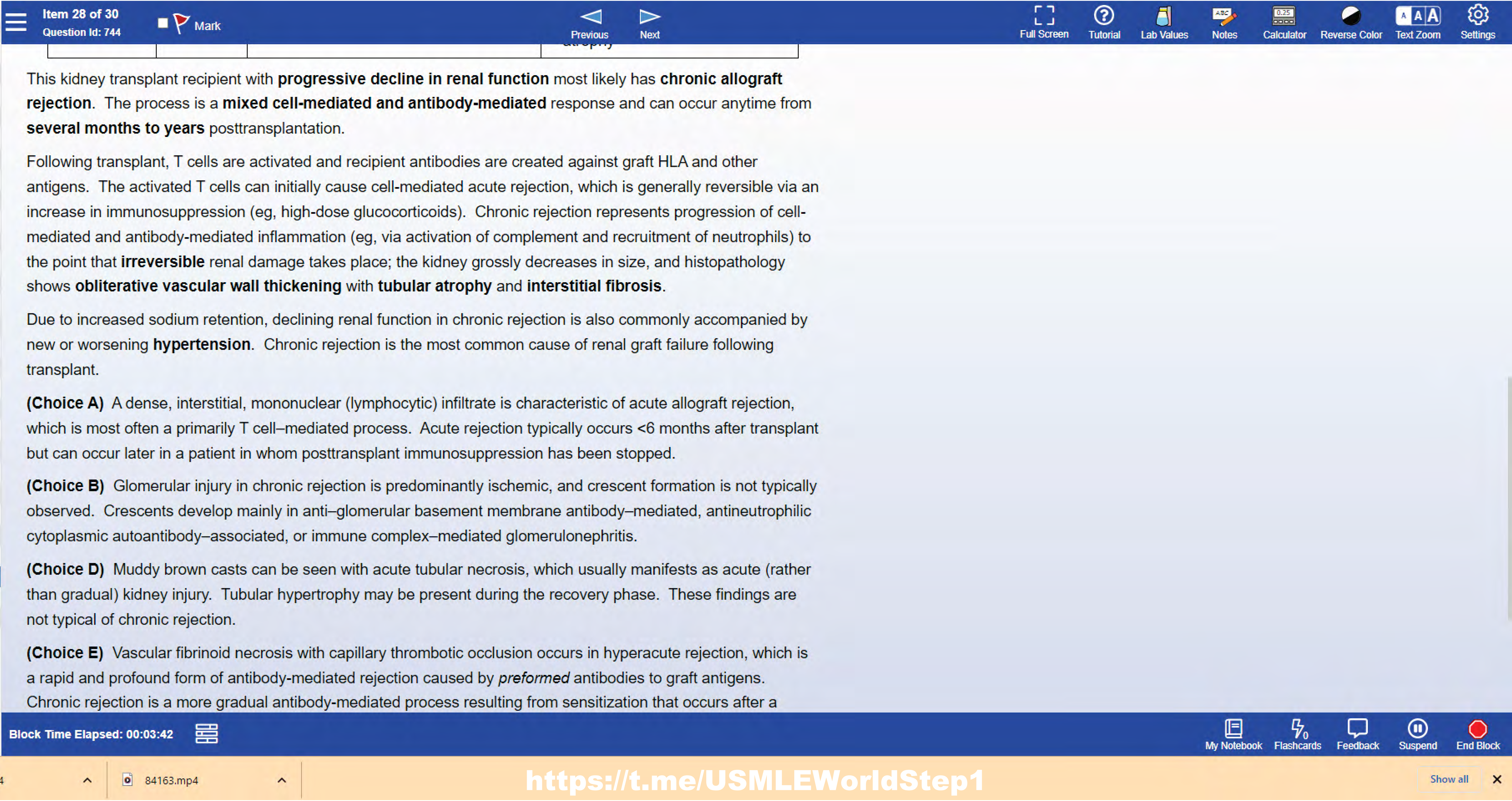

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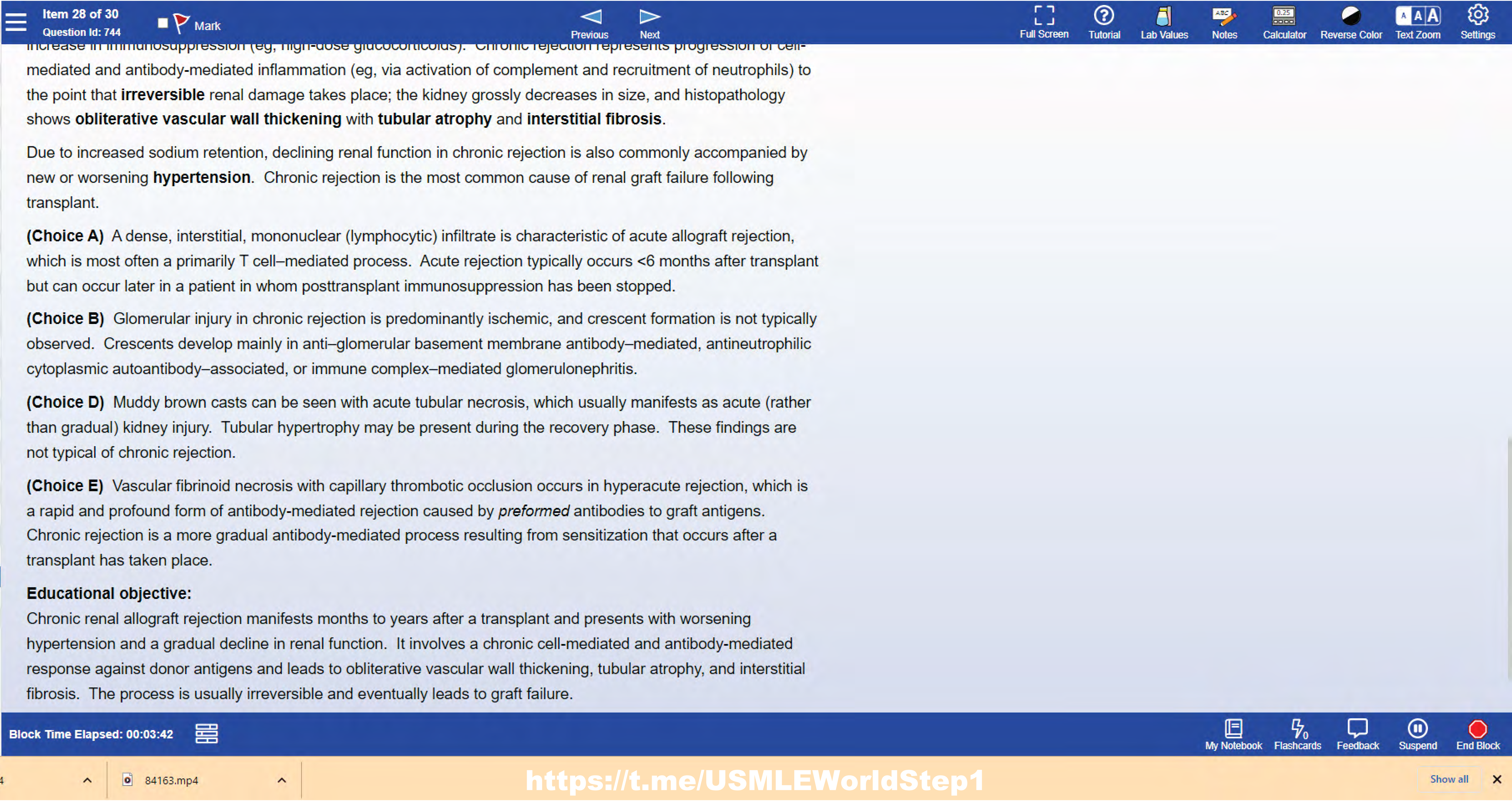
Due to increased sodium retention, declining renal function in chronic rejection is also commonly accompanied by new or worsening **hypertension**. Chronic rejection is the most common cause of renal graft failure following transplant.

(Choice A) A dense, interstitial, mononuclear (lymphocytic) infiltrate is characteristic of acute allograft rejection, which is most often a primarily T cell–mediated process. Acute rejection typically occurs <6 months after transplant but can occur later in a patient in whom posttransplant immunosuppression has been stopped.

(Choice B) Glomerular injury in chronic rejection is predominantly ischemic, and crescent formation is not typically observed. Crescents develop mainly in anti–glomerular basement membrane antibody–mediated, antineutrophilic cytoplasmic autoantibody–associated, or immune complex–mediated glomerulonephritis.

(Choice D) Muddy brown casts can be seen with acute tubular necrosis, which usually manifests as acute (rather than gradual) kidney injury. Tubular hypertrophy may be present during the recovery phase. These findings are not typical of chronic rejection.

(Choice E) Vascular fibrinoid necrosis with capillary thrombotic occlusion occurs in hyperacute rejection, which is a rapid and profound form of antibody-mediated rejection caused by *preformed* antibodies to graft antigens. Chronic rejection is a more gradual antibody-mediated process resulting from sensitization that occurs after a



increase in immunosuppression (eg, high-dose glucocorticoids). Chronic rejection represents progression of cell-mediated and antibody-mediated inflammation (eg, via activation of complement and recruitment of neutrophils) to the point that **irreversible** renal damage takes place; the kidney grossly decreases in size, and histopathology shows **obliterative vascular wall thickening** with **tubular atrophy** and **interstitial fibrosis**.

Due to increased sodium retention, declining renal function in chronic rejection is also commonly accompanied by new or worsening **hypertension**. Chronic rejection is the most common cause of renal graft failure following transplant.

(Choice A) A dense, interstitial, mononuclear (lymphocytic) infiltrate is characteristic of acute allograft rejection, which is most often a primarily T cell–mediated process. Acute rejection typically occurs <6 months after transplant but can occur later in a patient in whom posttransplant immunosuppression has been stopped.

(Choice B) Glomerular injury in chronic rejection is predominantly ischemic, and crescent formation is not typically observed. Crescents develop mainly in anti–glomerular basement membrane antibody–mediated, antineutrophilic cytoplasmic autoantibody–associated, or immune complex–mediated glomerulonephritis.

(Choice D) Muddy brown casts can be seen with acute tubular necrosis, which usually manifests as acute (rather than gradual) kidney injury. Tubular hypertrophy may be present during the recovery phase. These findings are not typical of chronic rejection.

(Choice E) Vascular fibrinoid necrosis with capillary thrombotic occlusion occurs in hyperacute rejection, which is a rapid and profound form of antibody-mediated rejection caused by *preformed* antibodies to graft antigens. Chronic rejection is a more gradual antibody-mediated process resulting from sensitization that occurs after a transplant has taken place.

Educational objective:
Chronic renal allograft rejection manifests months to years after a transplant and presents with worsening hypertension and a gradual decline in renal function. It involves a chronic cell-mediated and antibody-mediated response against donor antigens and leads to obliterative vascular wall thickening, tubular atrophy, and interstitial fibrosis. The process is usually irreversible and eventually leads to graft failure.

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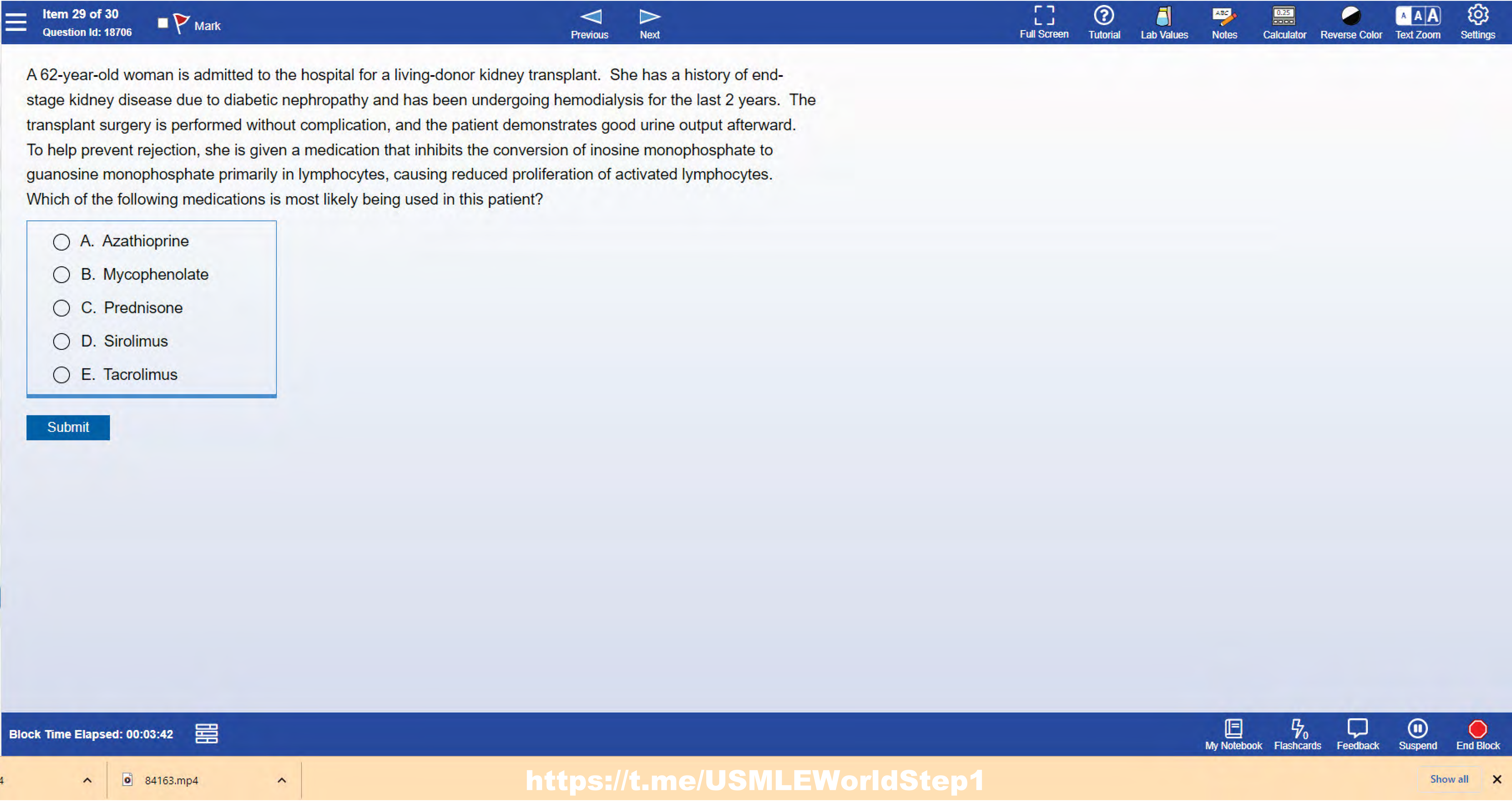
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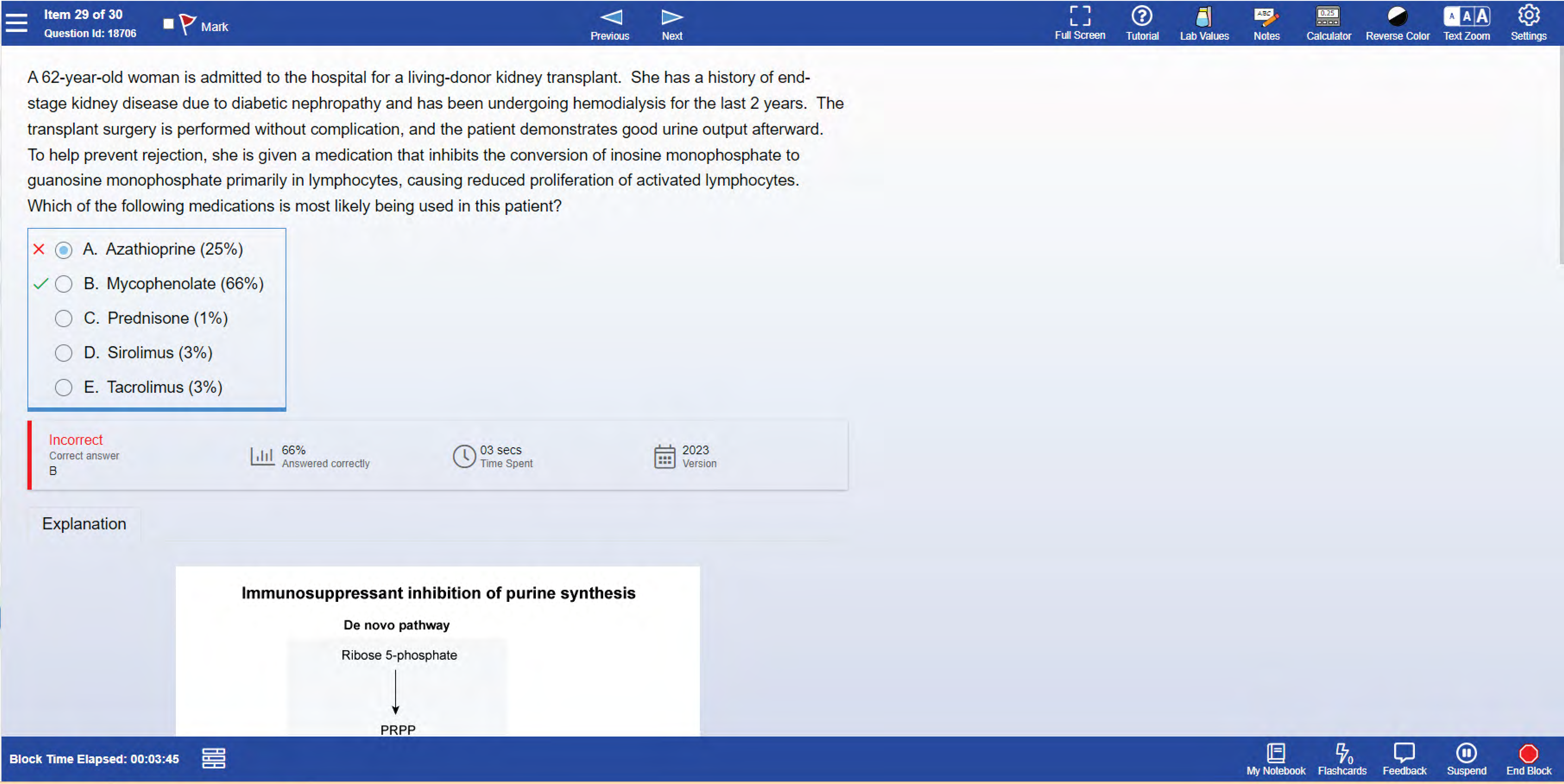
A 62-year-old woman is admitted to the hospital for a living-donor kidney transplant. She has a history of end-stage kidney disease due to diabetic nephropathy and has been undergoing hemodialysis for the last 2 years. The transplant surgery is performed without complication, and the patient demonstrates good urine output afterward. To help prevent rejection, she is given a medication that inhibits the conversion of inosine monophosphate to guanosine monophosphate primarily in lymphocytes, causing reduced proliferation of activated lymphocytes. Which of the following medications is most likely being used in this patient?

○ A. Azathioprine
○ B. Mycophenolate
○ C. Prednisone
○ D. Sirolimus
○ E. Tacrolimus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✗ ● A. Azathioprine (25%)
✓ ○ B. Mycophenolate (66%)
○ C. Prednisone (1%)
○ D. Sirolimus (3%)
○ E. Tacrolimus (3%)

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Correct answer
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Explanation

Immunosuppressant inhibition of purine synthesis

De novo pathway
Ribose 5-phosphate
PRPP
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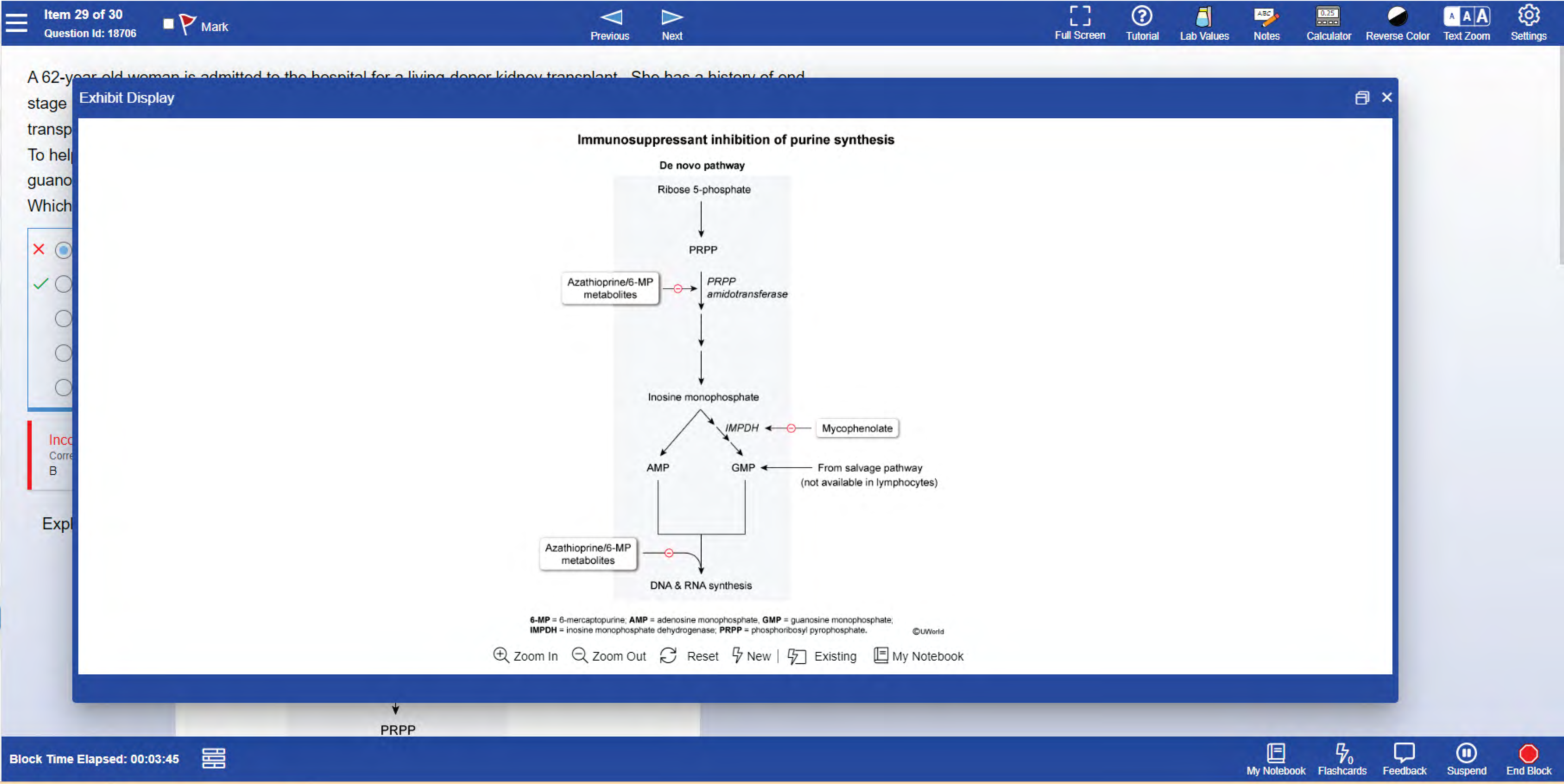
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Immunosuppressant inhibition of purine synthesis

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PRPP
Azathioprine/6-MP metabolites
PRPP amidotransferase
Inosine monophosphate
IMPDH
Mycophenolate
AMP
GMP
From salvage pathway (not available in lymphocytes)
Azathioprine/6-MP metabolites
DNA & RNA synthesis
PRPP

6-MP = 6-mercaptopurine; **AMP** = adenosine monophosphate; **GMP** = guanosine monophosphate; **IMPDH** = inosine monophosphate dehydrogenase; **PRPP** = phosphoribosyl pyrophosphate.

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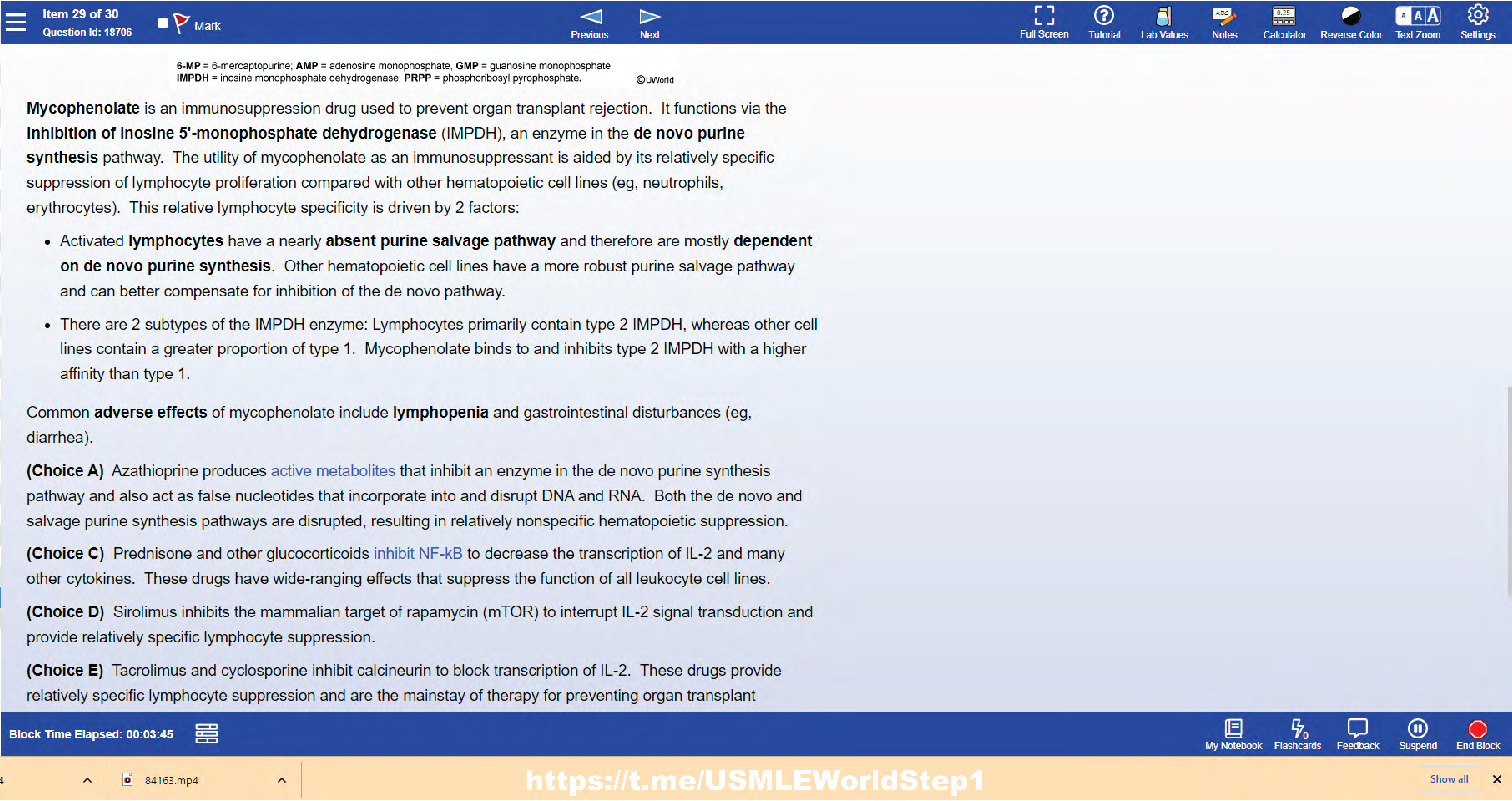

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IMPDH = inosine monophosphate dehydrogenase; **PRPP** = phosphoribosyl pyrophosphate.

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Mycophenolate is an immunosuppression drug used to prevent organ transplant rejection. It functions via the **inhibition of inosine 5'-monophosphate dehydrogenase** (IMPDH), an enzyme in the **de novo purine synthesis** pathway. The utility of mycophenolate as an immunosuppressant is aided by its relatively specific suppression of lymphocyte proliferation compared with other hematopoietic cell lines (eg, neutrophils, erythrocytes). This relative lymphocyte specificity is driven by 2 factors:

- Activated **lymphocytes** have a nearly **absent purine salvage pathway** and therefore are mostly **dependent on de novo purine synthesis**. Other hematopoietic cell lines have a more robust purine salvage pathway and can better compensate for inhibition of the de novo pathway.
- There are 2 subtypes of the IMPDH enzyme: Lymphocytes primarily contain type 2 IMPDH, whereas other cell lines contain a greater proportion of type 1. Mycophenolate binds to and inhibits type 2 IMPDH with a higher affinity than type 1.

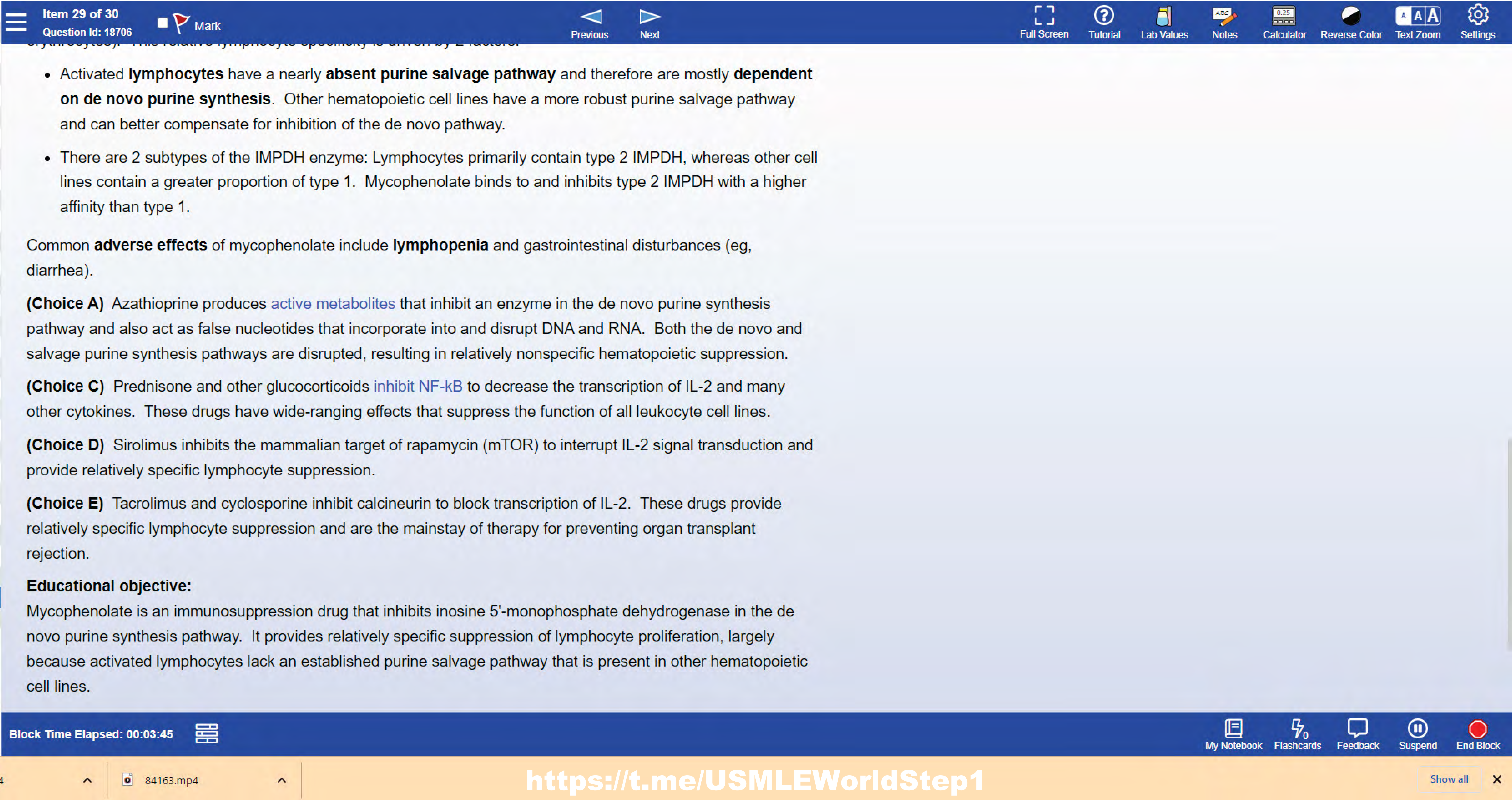
Common **adverse effects** of mycophenolate include **lymphopenia** and gastrointestinal disturbances (eg, diarrhea).

(Choice A) Azathioprine produces active metabolites that inhibit an enzyme in the de novo purine synthesis pathway and also act as false nucleotides that incorporate into and disrupt DNA and RNA. Both the de novo and salvage purine synthesis pathways are disrupted, resulting in relatively nonspecific hematopoietic suppression.

(Choice C) Prednisone and other glucocorticoids inhibit NF-kB to decrease the transcription of IL-2 and many other cytokines. These drugs have wide-ranging effects that suppress the function of all leukocyte cell lines.

(Choice D) Sirolimus inhibits the mammalian target of rapamycin (mTOR) to interrupt IL-2 signal transduction and provide relatively specific lymphocyte suppression.

(Choice E) Tacrolimus and cyclosporine inhibit calcineurin to block transcription of IL-2. These drugs provide relatively specific lymphocyte suppression and are the mainstay of therapy for preventing organ transplant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(Choice E) Tacrolimus and cyclosporine inhibit calcineurin to block transcription of IL-2. These drugs provide relatively specific lymphocyte suppression and are the mainstay of therapy for preventing organ transplant rejection.

Educational objective:
Mycophenolate is an immunosuppression drug that inhibits inosine 5'-monophosphate dehydrogenase in the de novo purine synthesis pathway. It provides relatively specific suppression of lymphocyte proliferation, largely because activated lymphocytes lack an established purine salvage pathway that is present in other hematopoietic cell lines.

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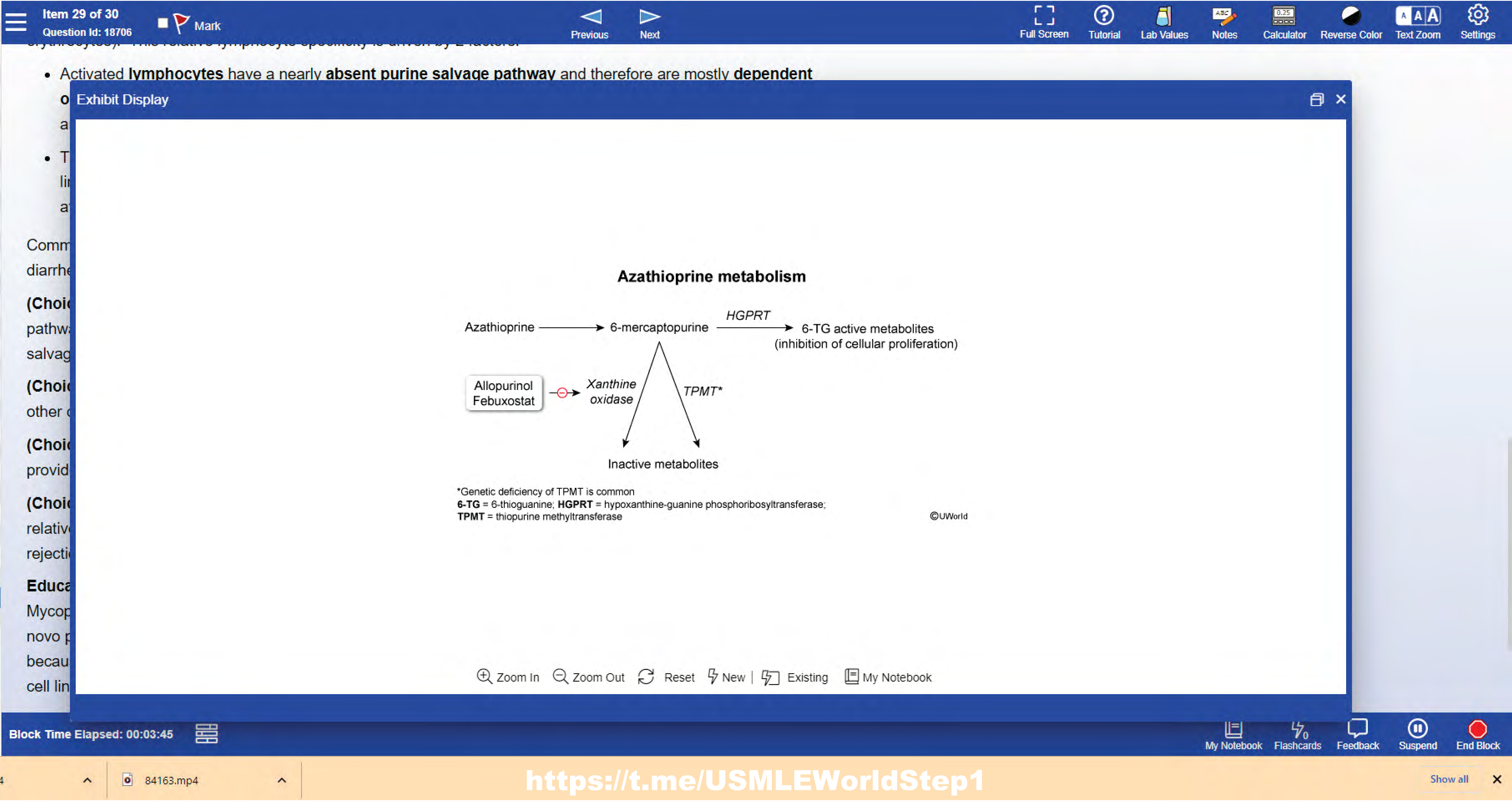
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Azathioprine metabolism

Azathioprine
6-mercaptopurine
HGPRT
6-TG active metabolites
(inhibition of cellular proliferation)
Allopurinol
Febuxostat
⊖
Xanthine
oxidase
TPMT*
Inactive metabolites

*Genetic deficiency of TPMT is common
6-TG = 6-thioguanine; **HGPRT** = hypoxanthine-guanine phosphoribosyltransferase;
TPMT = thiopurine methyltransferase

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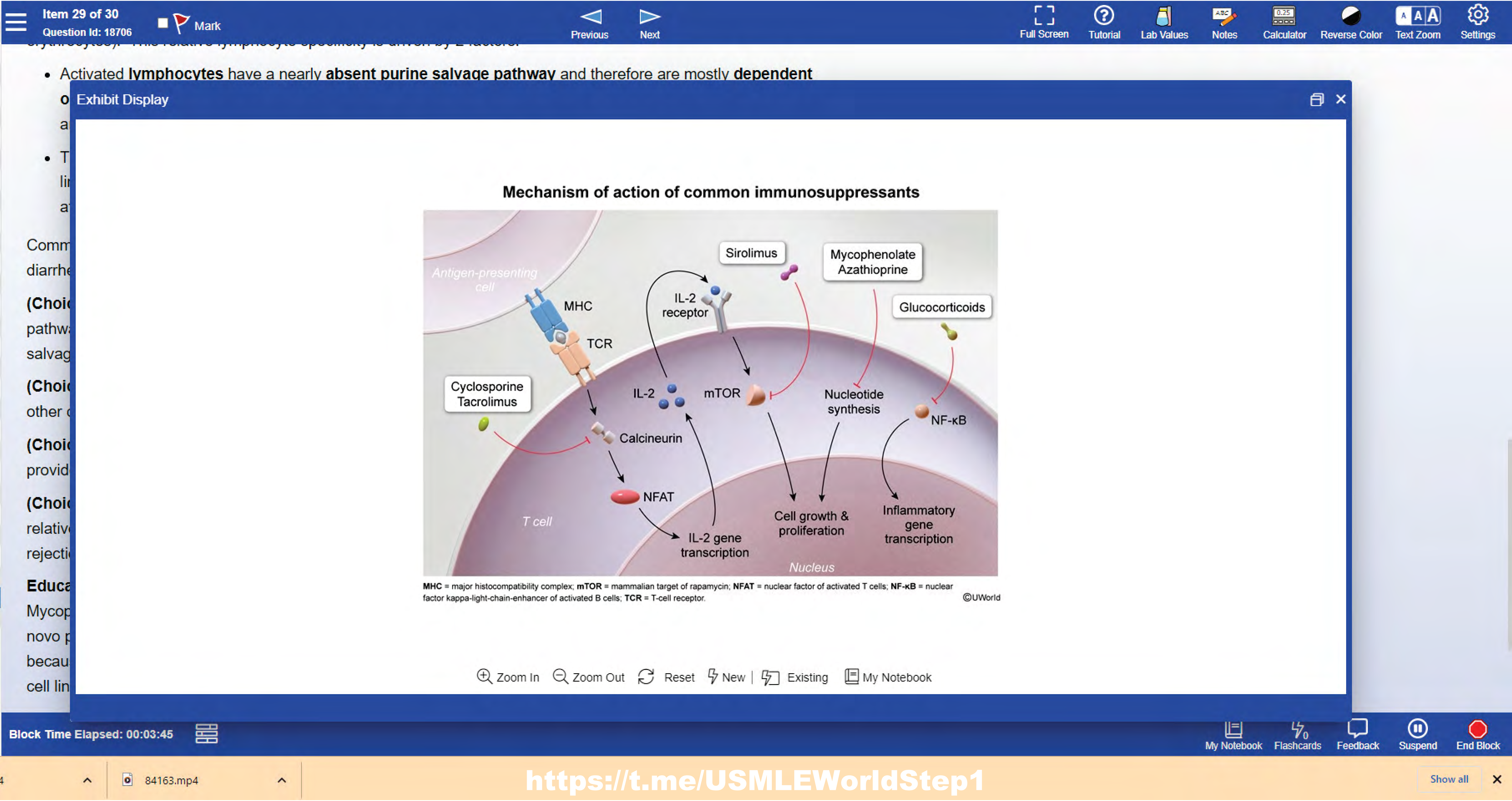
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Antigen-presenting cell
MHC
TCR
IL-2 receptor
Sirolimus
Mycophenolate
Azathioprine
Glucocorticoids
Cyclosporine
Tacrolimus
IL-2
mTOR
Nucleotide synthesis
NF-κB
Calcineurin
NFAT
T cell
IL-2 gene transcription
Cell growth & proliferation
Inflammatory gene transcription
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Mechanism of action of common immunosuppressants

MHC = major histocompatibility complex; **mTOR** = mammalian target of rapamycin; **NFAT** = nuclear factor of activated T cells; **NF-κB** = nuclear factor kappa-light-chain-enhancer of activated B cells; **TCR** = T-cell receptor.

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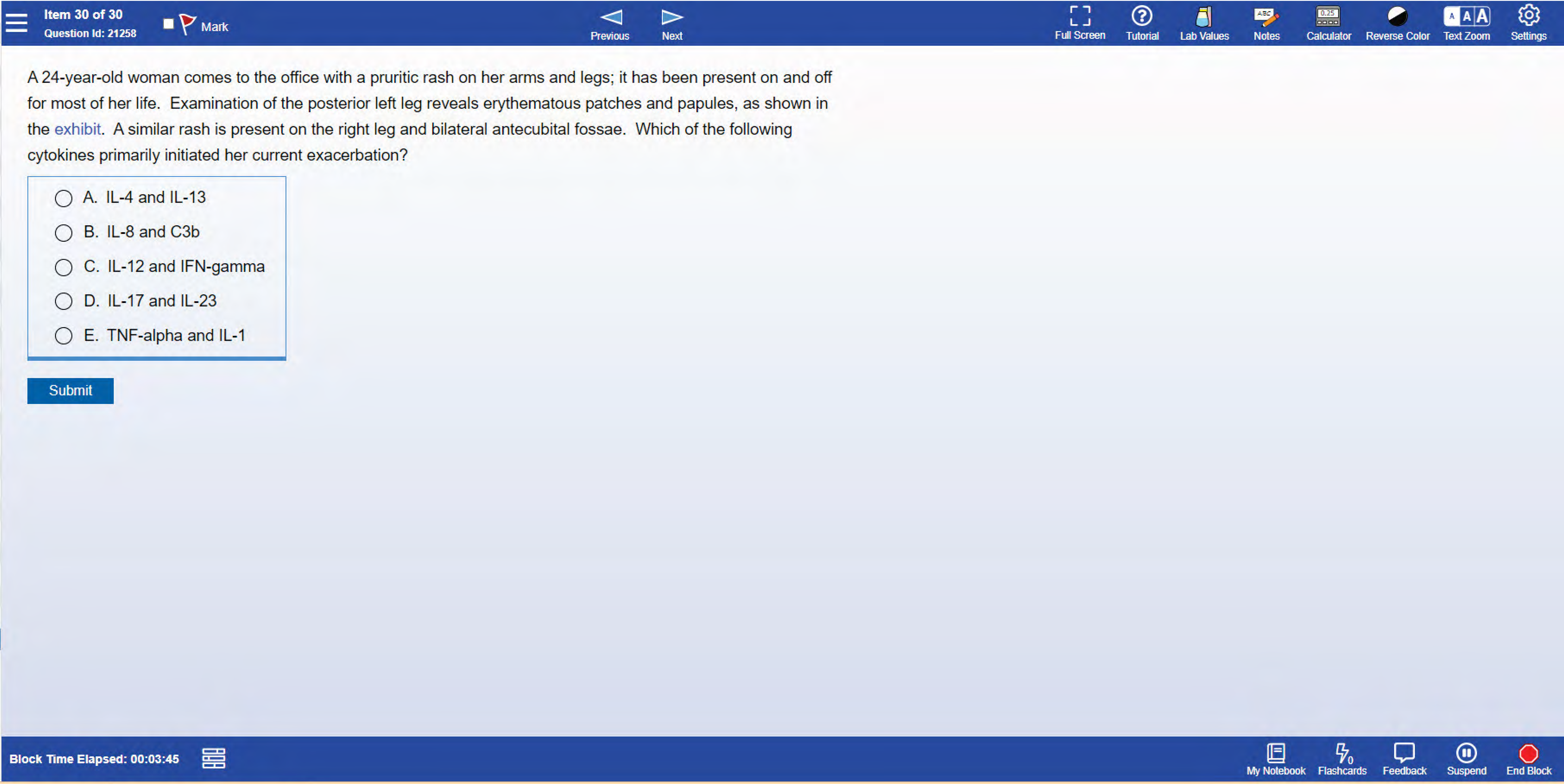
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A 24-year-old woman comes to the office with a pruritic rash on her arms and legs; it has been present on and off for most of her life. Examination of the posterior left leg reveals erythematous patches and papules, as shown in the exhibit. A similar rash is present on the right leg and bilateral antecubital fossae. Which of the following cytokines primarily initiated her current exacerbation?

- ○ A. IL-4 and IL-13
- ○ B. IL-8 and C3b
- ○ C. IL-12 and IFN-gamma
- ○ D. IL-17 and IL-23
- ○ E. TNF-alpha and IL-1

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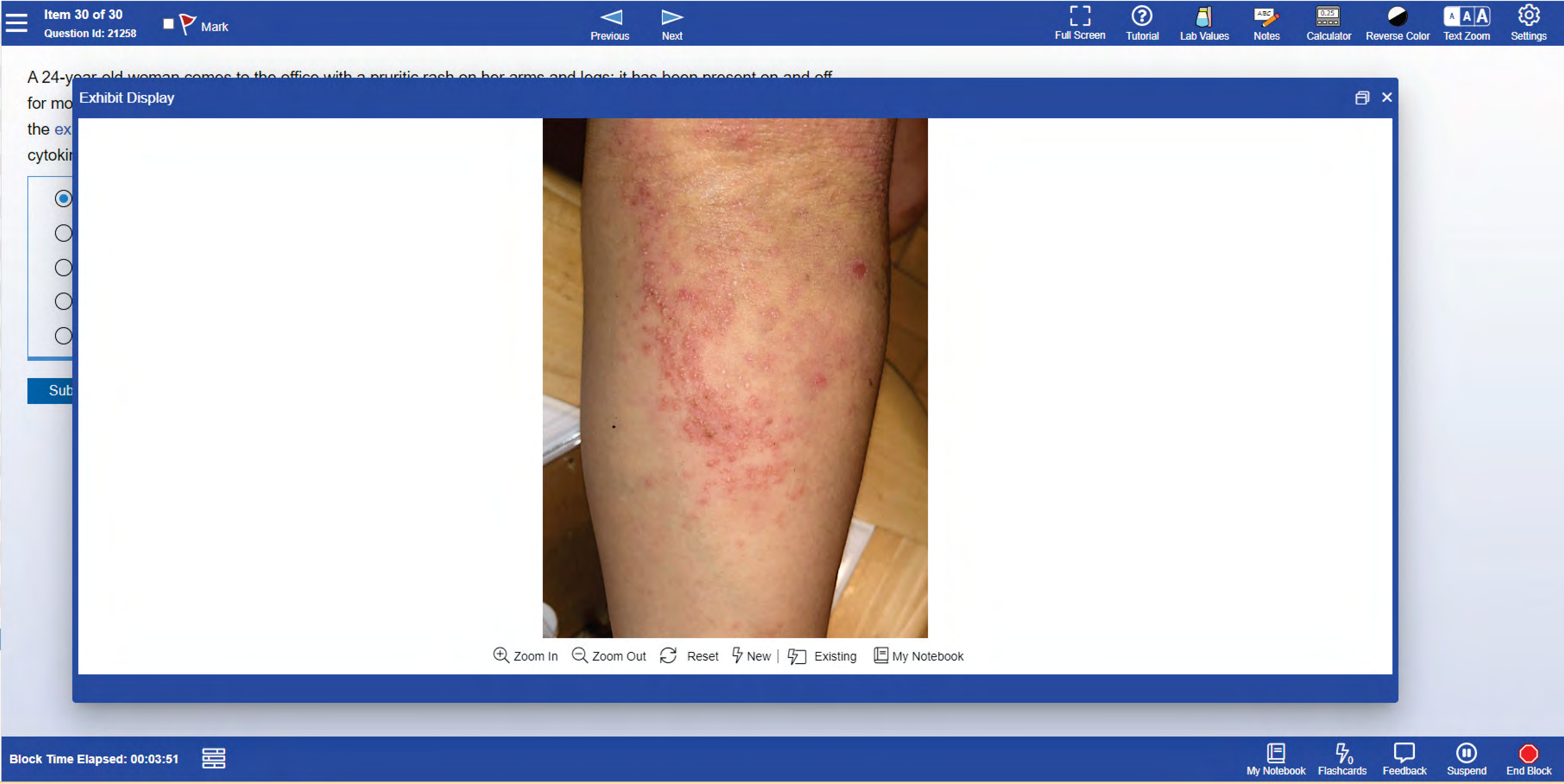
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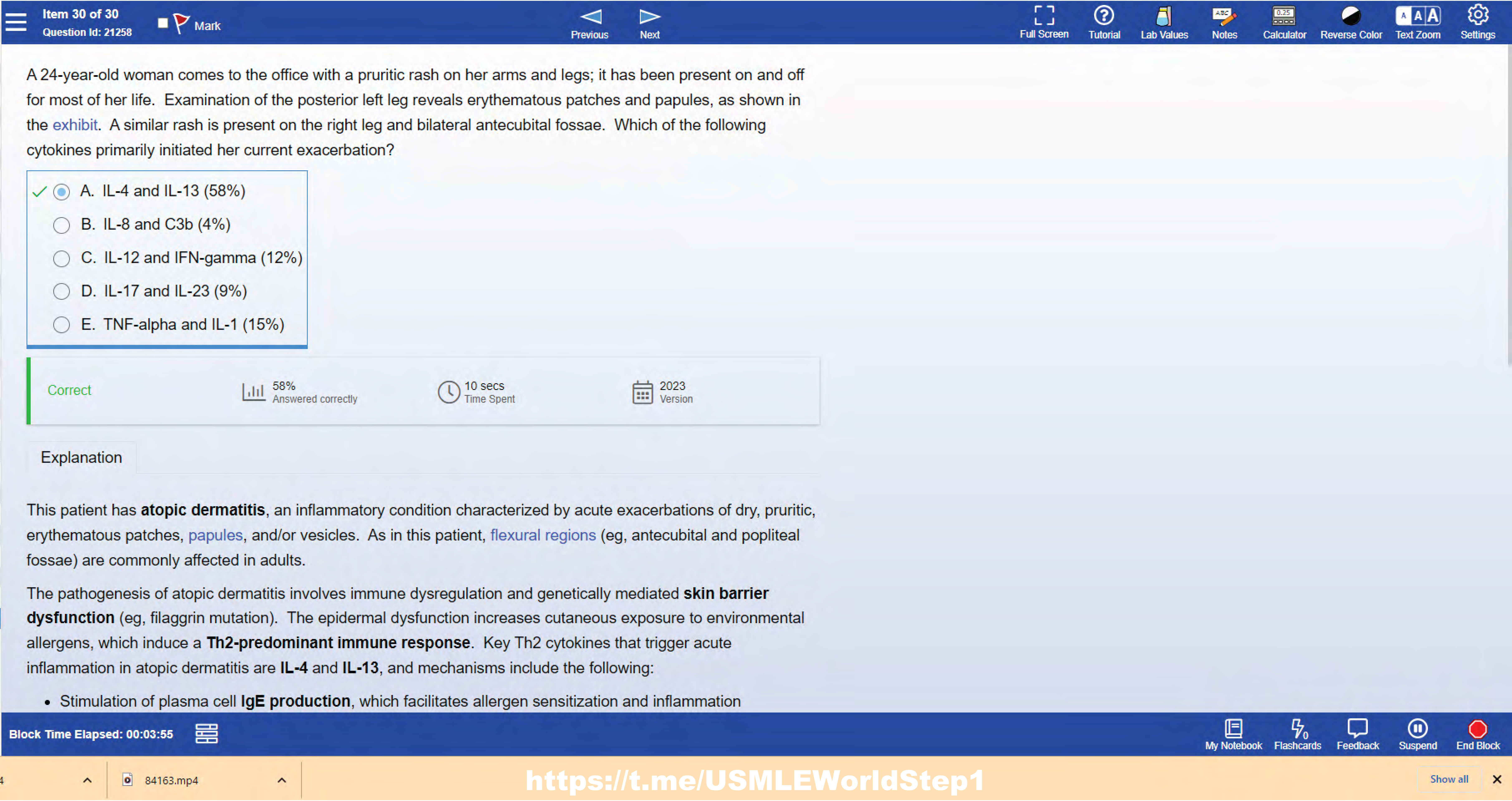
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✓ ● A. IL-4 and IL-13 (58%)
○ B. IL-8 and C3b (4%)
○ C. IL-12 and IFN-gamma (12%)
○ D. IL-17 and IL-23 (9%)
○ E. TNF-alpha and IL-1 (15%)

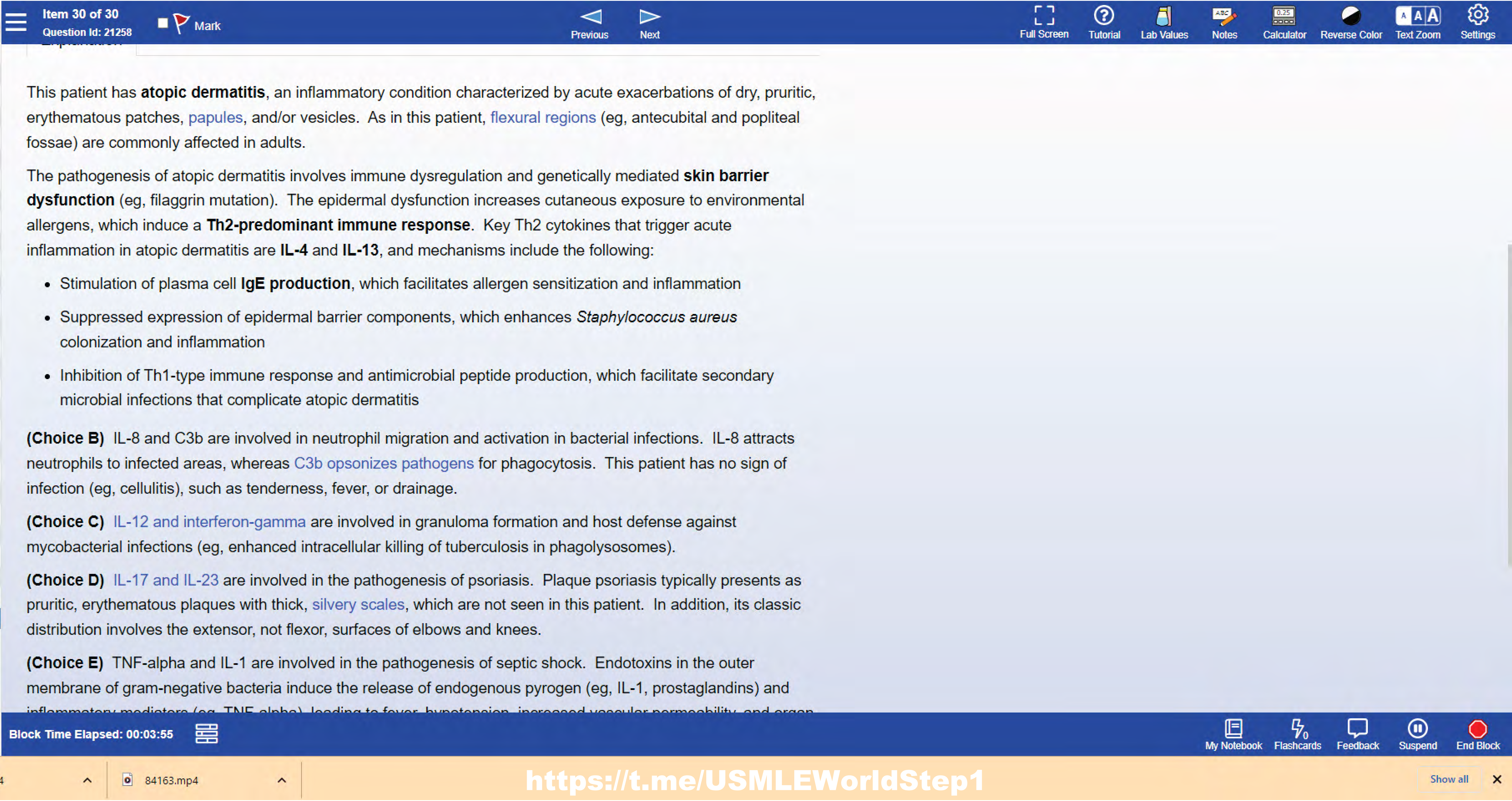
Correct | 58% Answered correctly | 10 secs Time Spent | 2023 Version

Explanation

This patient has **atopic dermatitis**, an inflammatory condition characterized by acute exacerbations of dry, pruritic, erythematous patches, papules, and/or vesicles. As in this patient, flexural regions (eg, antecubital and popliteal fossae) are commonly affected in adults.

The pathogenesis of atopic dermatitis involves immune dysregulation and genetically mediated **skin barrier dysfunction** (eg, filaggrin mutation). The epidermal dysfunction increases cutaneous exposure to environmental allergens, which induce a **Th2-predominant immune response**. Key Th2 cytokines that trigger acute inflammation in atopic dermatitis are **IL-4** and **IL-13**, and mechanisms include the following:

- Stimulation of plasma cell **IgE production**, which facilitates allergen sensitization and inflammation



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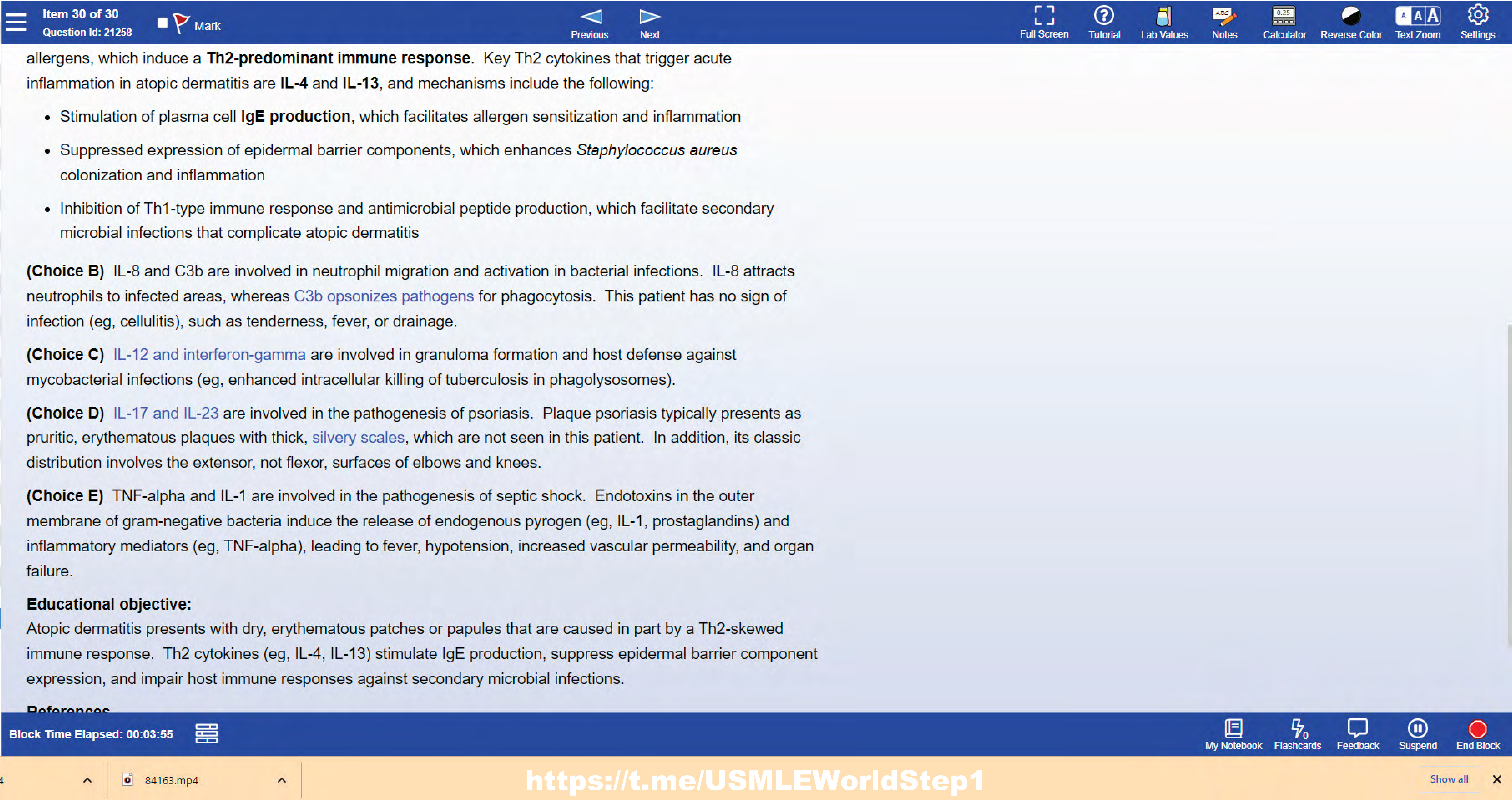
- Stimulation of plasma cell **IgE production**, which facilitates allergen sensitization and inflammation
- Suppressed expression of epidermal barrier components, which enhances *Staphylococcus aureus* colonization and inflammation
- Inhibition of Th1-type immune response and antimicrobial peptide production, which facilitate secondary microbial infections that complicate atopic dermatitis

(Choice B) IL-8 and C3b are involved in neutrophil migration and activation in bacterial infections. IL-8 attracts neutrophils to infected areas, whereas C3b opsonizes pathogens for phagocytosis. This patient has no sign of infection (eg, cellulitis), such as tenderness, fever, or drainage.

(Choice C) IL-12 and interferon-gamma are involved in granuloma formation and host defense against mycobacterial infections (eg, enhanced intracellular killing of tuberculosis in phagolysosomes).

(Choice D) IL-17 and IL-23 are involved in the pathogenesis of psoriasis. Plaque psoriasis typically presents as pruritic, erythematous plaques with thick, silvery scales, which are not seen in this patient. In addition, its classic distribution involves the extensor, not flexor, surfaces of elbows and knees.

(Choice E) TNF-alpha and IL-1 are involved in the pathogenesis of septic shock. Endotoxins in the outer membrane of gram-negative bacteria induce the release of endogenous pyrogen (eg, IL-1, prostaglandins) and inflammatory mediators (eg, TNF-alpha) leading to fever, hypotension, increased vascular permeability, and organ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Educational objective:

Atopic dermatitis presents with dry, erythematous patches or papules that are caused in part by a Th2-skewed immune response. Th2 cytokines (eg, IL-4, IL-13) stimulate IgE production, suppress epidermal barrier component expression, and impair host immune responses against secondary microbial infections.

References

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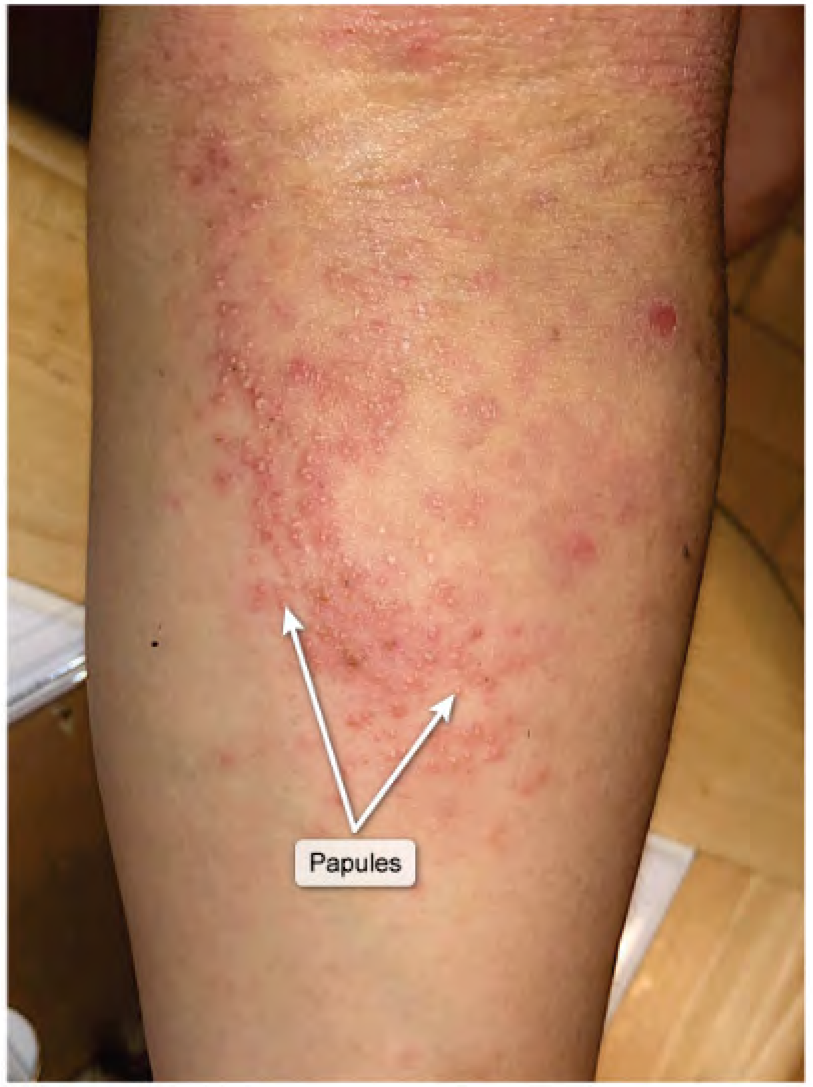
Atopic dermatitis (papular variant)



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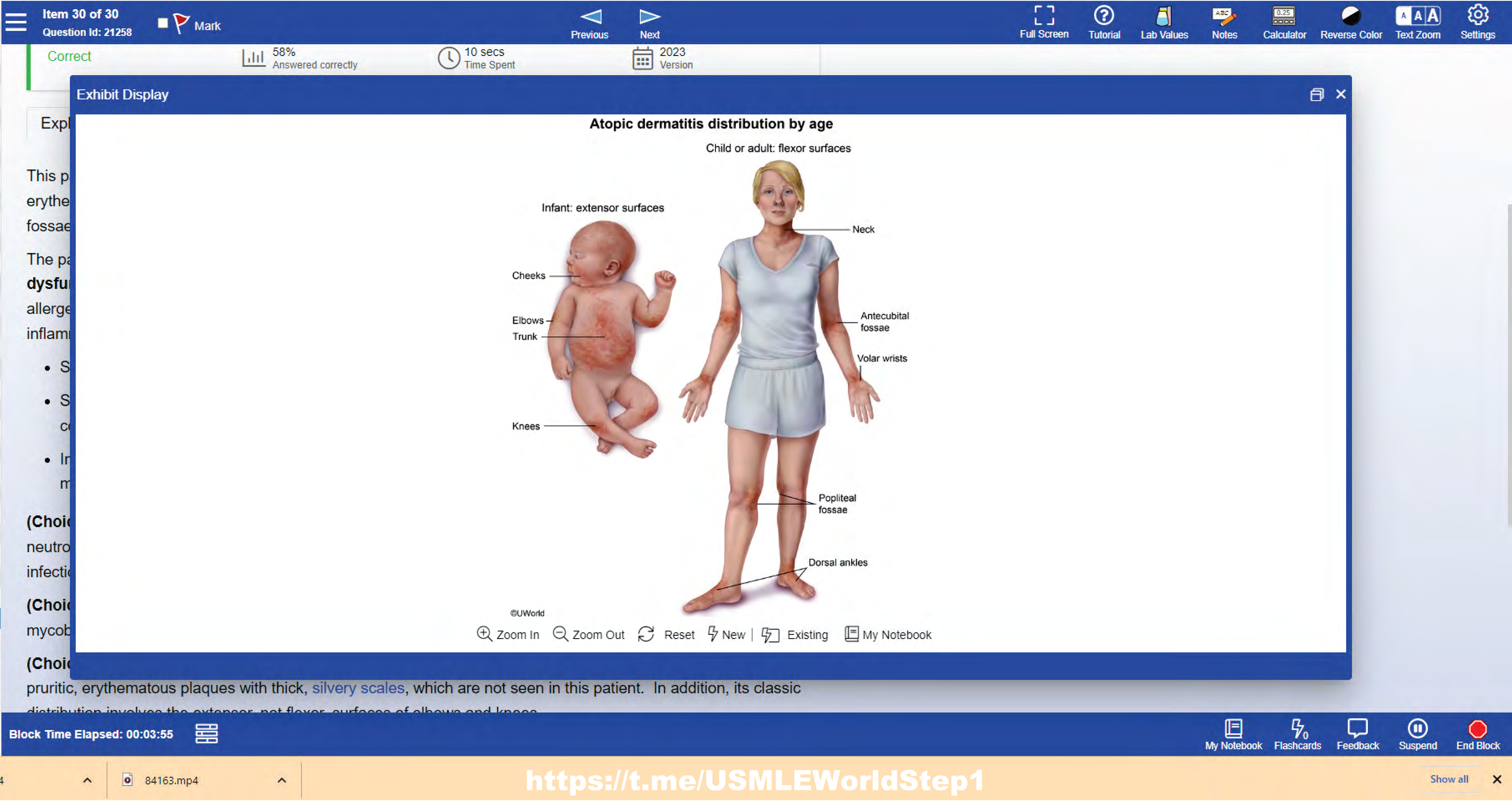
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Atopic dermatitis distribution by age
Child or adult: flexor surfaces
Infant: extensor surfaces
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Volar wrists
Popliteal fossae
Dorsal ankles
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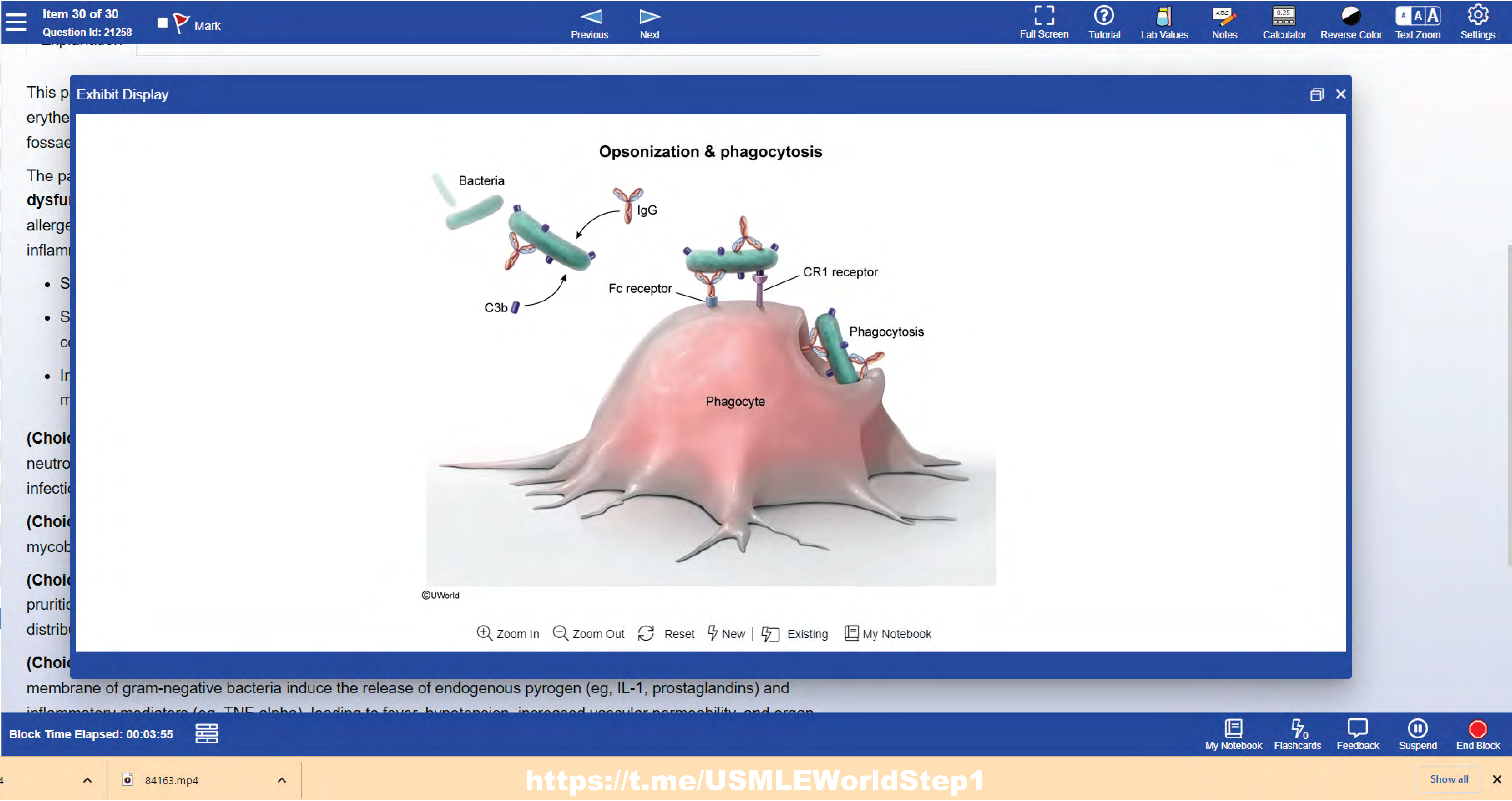
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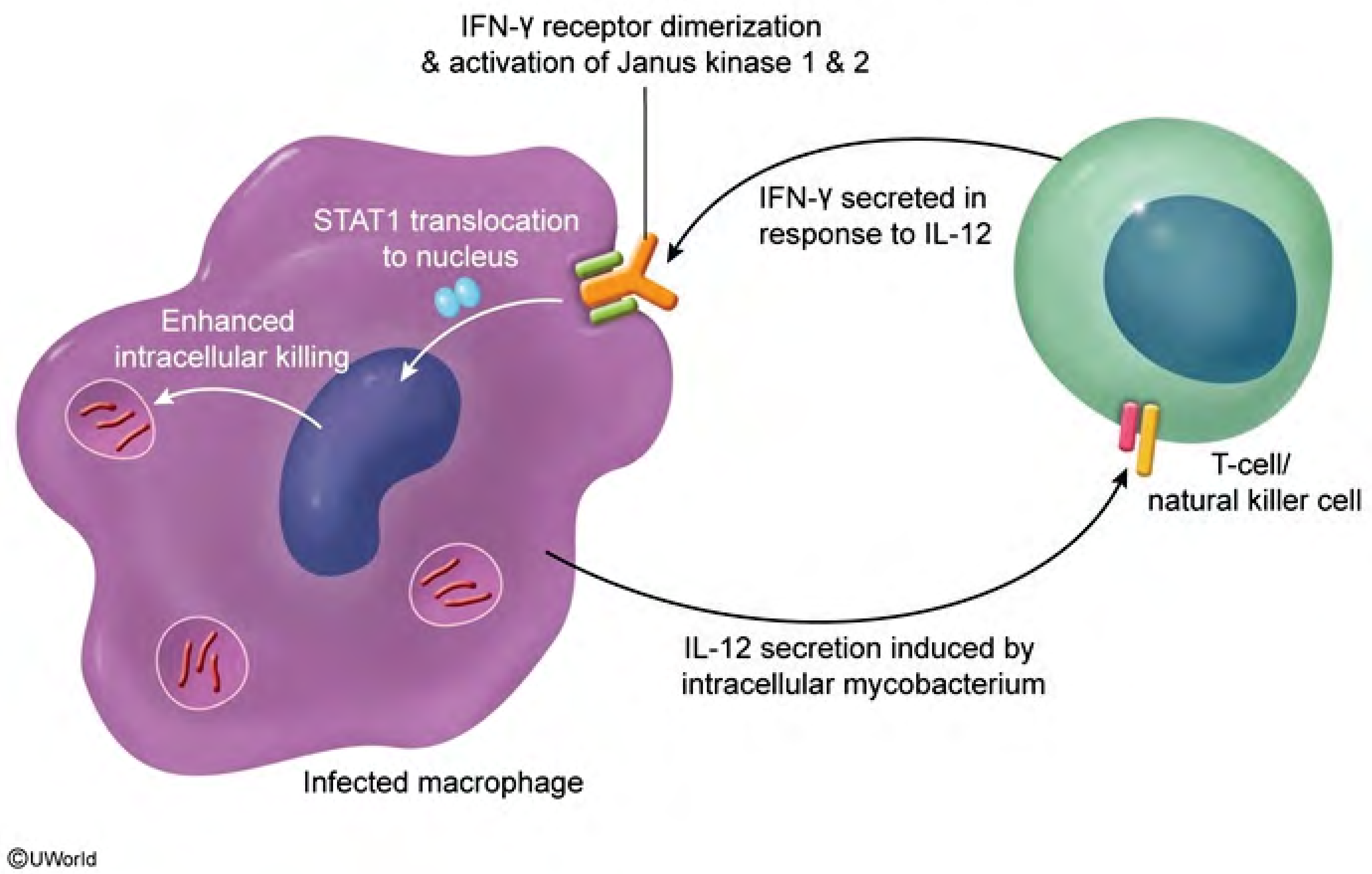
Interferon-gamma signaling pathway


IFN-ϒ receptor dimerization
& activation of Janus kinase 1 & 2
IFN-ϒ secreted in
response to IL-12
STAT1 translocation
to nucleus
Enhanced
intracellular killing
T-cell/
natural killer cell
IL-12 secretion induced by
intracellular mycobacterium
Infected macrophage
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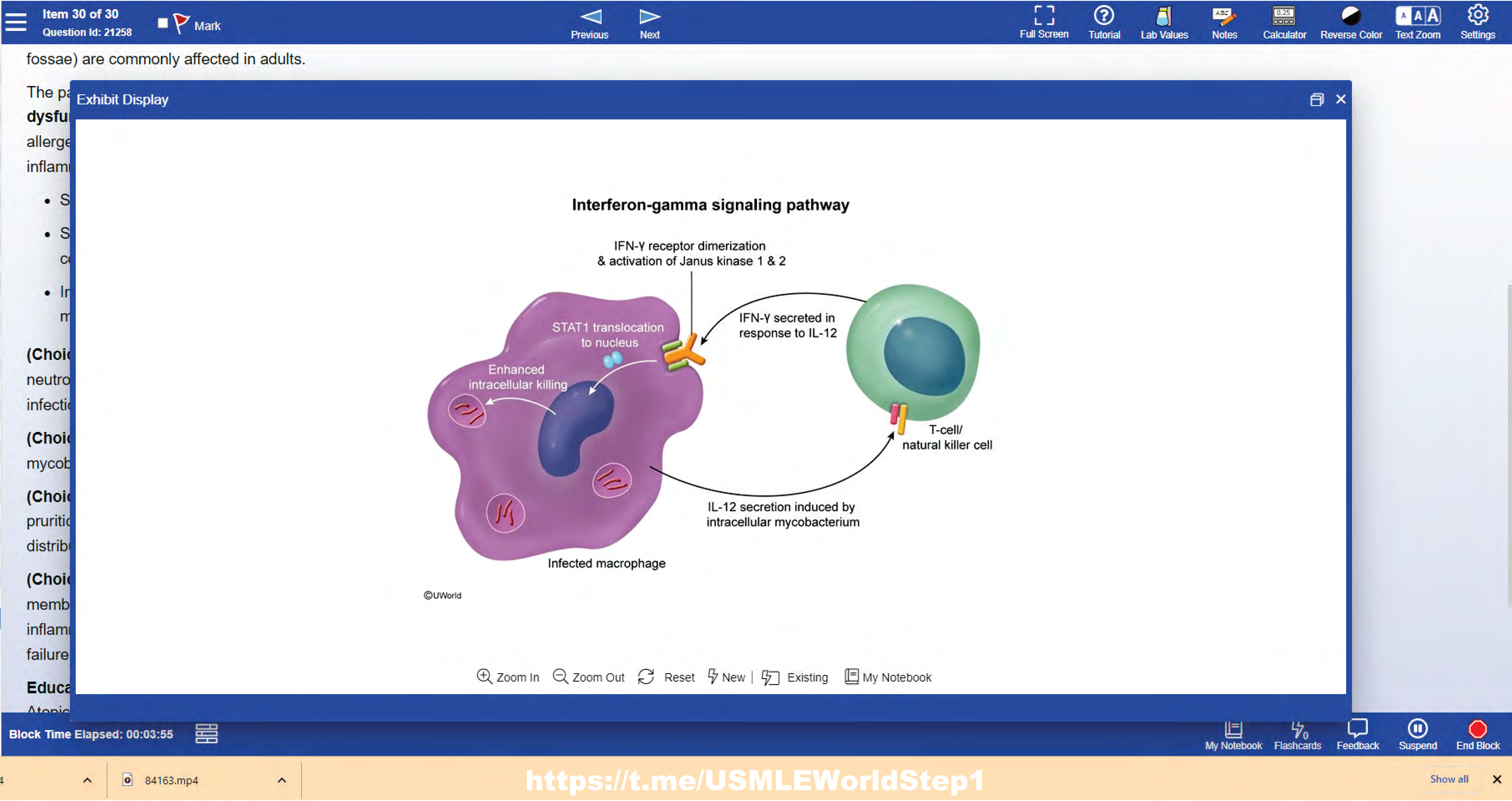

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Atopic

Exhibit Display

Interferon-gamma signaling pathway

IFN-γ receptor dimerization
& activation of Janus kinase 1 & 2
STAT1 translocation
to nucleus
Enhanced
intracellular killing
IFN-γ secreted in
response to IL-12
T-cell/
natural killer cell
IL-12 secretion induced by
intracellular mycobacterium
Infected macrophage
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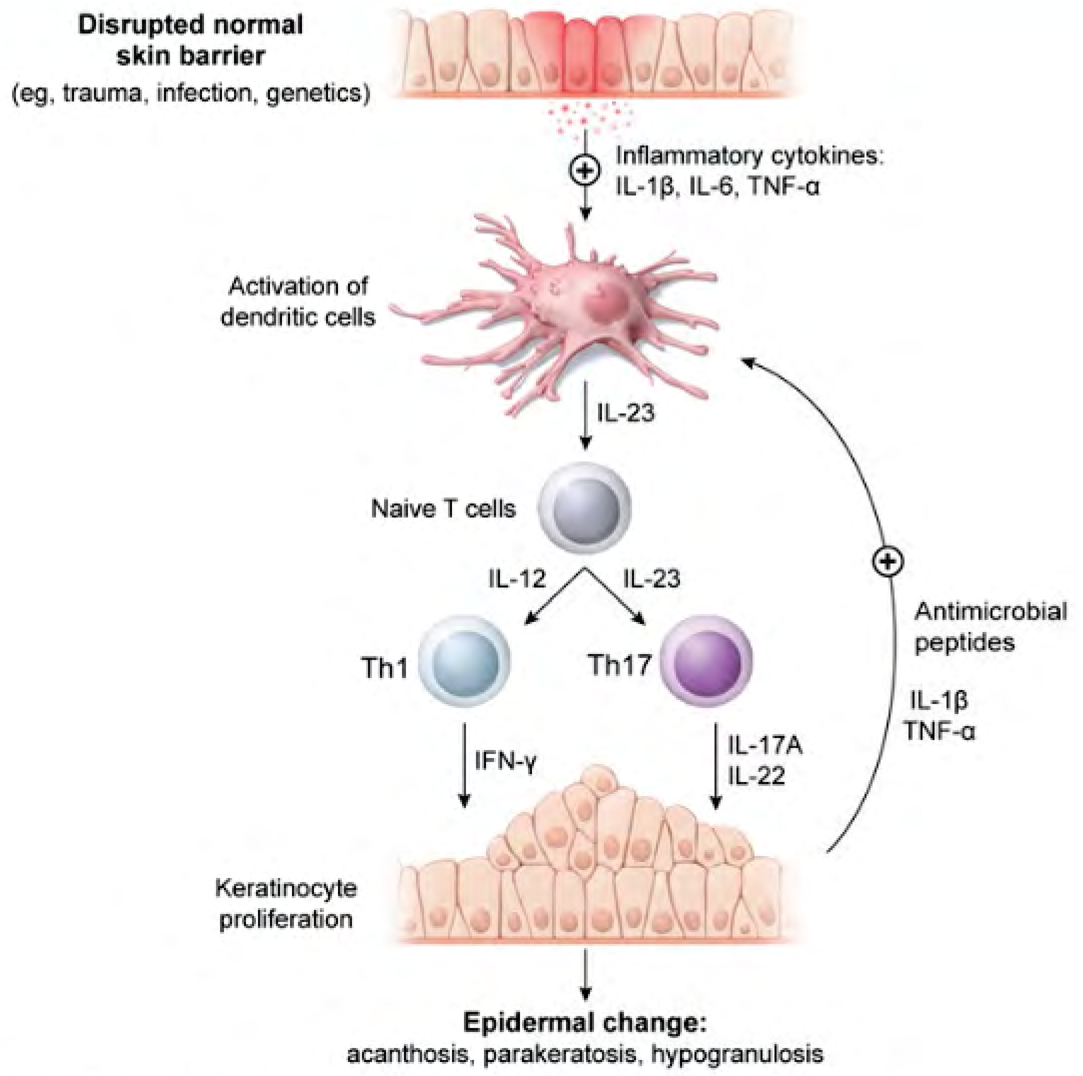
Pathophysiology of psoriasis


Disrupted normal skin barrier
(eg, trauma, infection, genetics)
Inflammatory cytokines:
IL-1β, IL-6, TNF-α
Activation of dendritic cells
IL-23
Naive T cells
IL-12
IL-23
Th1
Th17
IFN-γ
IL-17A
IL-22
Antimicrobial peptides
IL-1β
TNF-α
Keratinocyte proliferation
Epidermal change:
acanthosis, parakeratosis, hypogranulosis

IFN = interferon; **TNF** = tumor necrosis factor.

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Educational objective:

Atopic dermatitis presents with dry, erythematous patches or papules that are caused in part by a Th2-skewed

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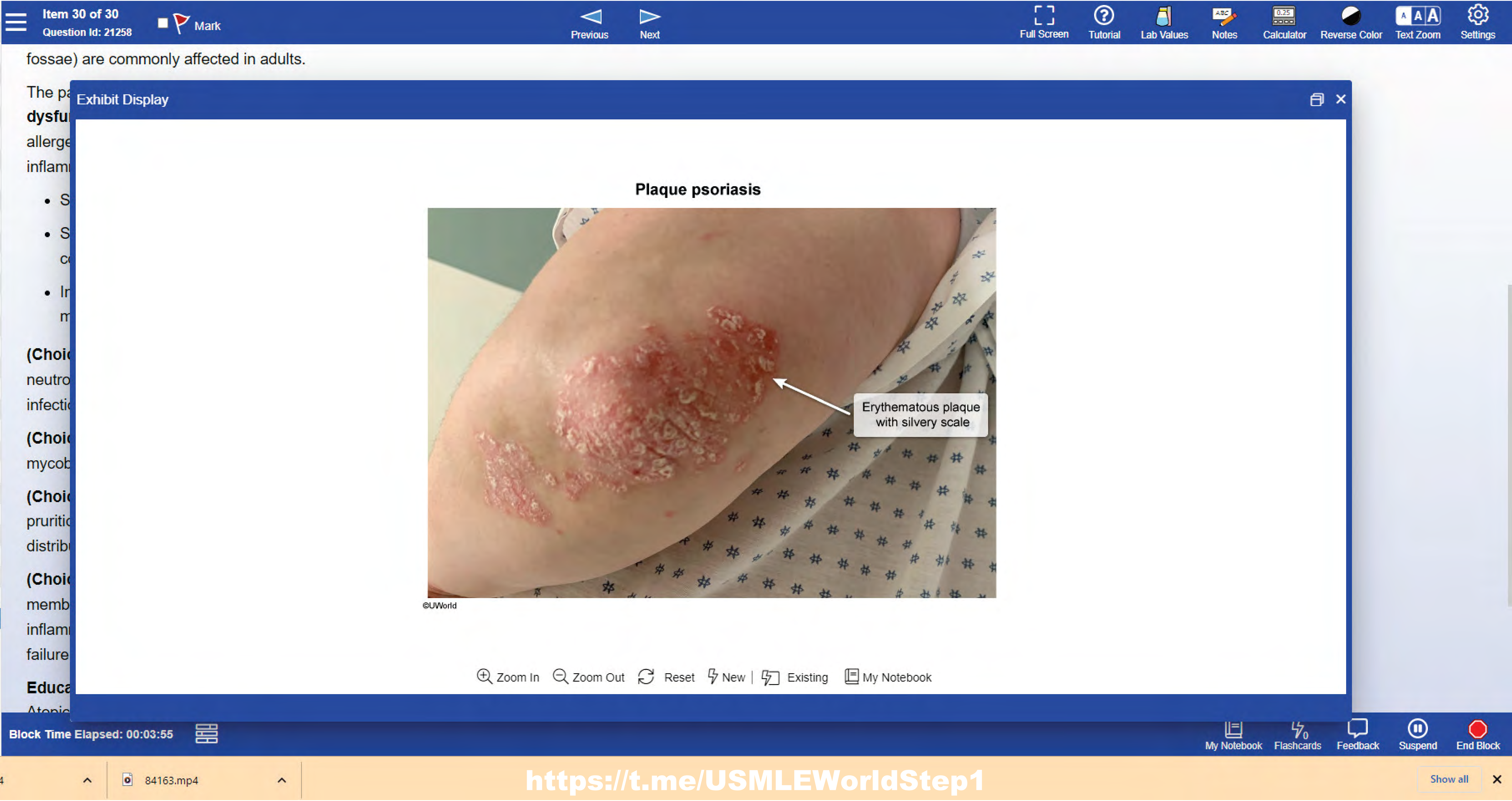
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Plaque psoriasis

Erythematous plaque with silvery scale

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